IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	Cavaleri et al.	:	Confirmation No.: 6785
APPLICATION NO.:	10/829,068	:	Examiner: E. Peselev
FILING DATE:	April 20, 2004	:	Group Art Unit: 1623
TITLE:	STABLE COMPOSITIONS OF DALBAVANCIN	:	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER RULE 1.132

I, Paul Luner, declare that:

1. I received a B.S. in Chemistry in 1984 from Syracuse University, and an M.S. (1986) and Ph.D. (1990) in Pharmaceutics from the University of Michigan, College of Pharmacy. From 1990 to 1995 I worked for Parke-Davis/Warner-Lambert Co. in the area of pharmaceutical preformulation and physical characterization. From 1995 through 2001 I was an Assistant Professor of Pharmaceutics at the University of Iowa, College of Pharmacy where my research included characterization of pharmaceutical materials and the influence of gastrointestinal environment on active pharmaceutical ingredients (API) and dosage forms (drug product). In 2002 I joined the Solids Development group within Pharmaceutical Research and Development at Pfizer where I was responsible for immediate release tablet formulation development (Phase I through Commercial Phase) and the utilization of small-scale techniques in formulation development. From 2006 until the present I have been responsible for solid state characterization and crystal form screening and salt selection for early and late-stage compounds including dalbavancin API and drug product. I have contributed several monographs to the Handbook of Pharmaceutical Excipients and have been a reviewer for journals including *Pharmaceutical Research*, *Journal of Pharmaceutical Sciences* and *Colloids and Surfaces*. I consider myself one of ordinary skill in the art of pharmaceutical sciences.

2. I have read the specification of the subject application and understand the amended claims to cover a pharmaceutical composition comprising dalbavancin containing MAG in an amount of less than about 3 mole percent; at least one stabilizer, wherein said stabilizer inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials; wherein the composition is lyophilized; and wherein the lyophilized pharmaceutical composition has a pH from about 3 to about 5 when reconstituted with water.

3. I have read the Office Action mailed January 31, 2008 for the subject application ("the January 31, 2008 Office Action"), in which the Examiner rejected claims 65 to 71 as being obvious over U.S. Patent No.

4. 5,750,509 to Malabarba ("the '509 Malabarba Patent").

5. On page 3 of the January 31, 2008 Office Action the Examiner asserts that the '509 Malabarba Patent discloses dalbavancin, a composition comprising a dalbavancin derivative and a stabilizer, and a composition in the form of a powder." The Examiner states

> Based on the teaching of Malabarba et al, it would have been prima facie obvious to a person having ordinary skill in the art at the time the claimed invention was made to combine dalbavancin with a stabilizer in order to produce a more stable composition. Further the resulting pH of said composition would be expected to be around 3.01. (Note the statement in the U.S. Patent No. 7,119,061 in column 23, lines 30-34 that a dalbavancin composition which has not been pH adjusted has a pH of about 3.01).

6. I have reviewed the '509 Malabarba Patent which was cited by the Examiner in the January 31, 2008 Office Action, and I discuss in the paragraphs 6-8 below. I discuss the '061 Stogniew Patent in paragraphs 9-14 below.

7. I first note that the '509 Malabarba Patent is concerned with the preparation of compounds or Active Pharmaceutical Ingredients ("APIs"), not pharmaceutical formulations; it only refers to formulating APIs as pharmaceutical formulations in a non-specific and very general manner. APIs are typically combined with excipients, or non-pharmacologically active components, to create a dosage form that can effectively deliver the API to the patient. Formulation components are selected for a variety of reasons including, for example, to aid the absorption or delivery of the API, to improve API chemical or physical stability, to enable or improve manufacturability, to extend shelf-life or obtain flexibility in storage conditions, to improve patient compliance, and to achieve container or packaging compatibility. The selection of the specific excipients for inclusion in a formulation will depend on many factors, including but not limited to, the chemical and physical properties of the API, the nature of the route of delivery and the manufacturing process for the dosage form. Optimization of the formulation often requires an appropriate balance of properties to yield a commercially acceptable product that meets regulatory specifications and meets predetermined standards of safety and efficacy. The means to achieve these characteristics in a dalbavancin-containing formulation requires extensive experimentation, testing and analysis for the reasons discussed below.

8. I also note that the '509 Malabarba Patent does not provide any discussion about the effect of pH on the stability of the isolated forms of dalbavancin API or lyophilized pharmaceutical compositions containing dalbavancin API. As one skilled in the art, I note that the preparation of a pharmaceutically acceptable lyophilized composition requires consideration of numerous factors including,

but not limited to: amount of API, whether the API is ionizable , whether it is an acid or a base, the counter-ion if it is a salt, the desired container physical characteristics, the glass transition temperature of the lyophile, eutectic temperature, the solubility of the API in the pre-lyophilized solution and the pH of that solution, temperature effect on solubility of the API in the solution to be lyophilized, thermal properties of the frozen solution, the tendency of the formulation to crystallize and the influence of the formulation components on crystallization, degree of supercooling in the process, achieving the desired solid content for the product after freeze drying, the physical and chemical stability of the lyophile during storage, the type and amount of liquid required to reconstitute the lyophile, the freeze drying process parameters that result in a lyophile with appropriate properties, the dissolution rate of the formulation, and residual moisture content.

9. The claims of the subject application claim a lyophilizing composition. Lyophilizing (freeze drying) involves many processing steps including, for example, solution formation and filtration, cooling and freezing, ice sublimation, annealing and secondary drying. The composition of the formulation may impact any of these process steps - and may also affect chemical stability. Therefore, selection of the formulation composition along with the processing conditions can greatly impact the performance properties of the final lyophile. I also note that changing one parameter in a pharmaceutical formulation often has an adverse affect on another property, so a pharmaceutical formulator needs to investigate and adjust a number of parameters in order to obtain a pharmaceutical composition which exhibits the proper balance of physical and chemical properties including product stability. Dalbavancin presents additional challenges, because its *solubility* decreases at high pH (e.g., above pH 7) while its *stability* decreases at low pH. Lastly, once all of the above physical and chemical properties of the formulation have been addressed, the composition must still be suitable for administration to a patient including having appropriate properties of tonicity and only containing components that are widely accepted by regulatory agencies. Thus, the cursory or general reference to the "various dosage forms" at col. 27, line 50 of the '509 Malabarba Patent and the limited description of formulation methods in their most general sense provides no guidance or discriminatory evaluation of the components mentioned therein, to make or use a dalbavancin composition having a pH from about 3 to about 5 with a stabilizer that inhibits degradation. The '509 Malabarba patent does not provide any compositional information that obviates the need to critically test compositions for compatibility and their advantages.

10. The '061 Stogniew Patent referred to by the Examiner in the January 31, 2008 Office Action differs from the '509 Malabarba Patent in that it relates to pharmaceutical compositions containing dalbavancin API. The '061 Stogniew Patent shows that the dalbavancin API in such pharmaceutical compositions tends to degrade into other non-dalbavancin components as the compositions become more acidic, that is, have a lower pH of reconstitution (as discussed in paragraph 14 below). However, the '061 Stogniew Patent also shows that the degradation of the dalbavancin API can be inhibited by formulating the acidic

dalbavancin compositions with a stabilizer that inhibits (or reduces the rate of) the formation of non-dalbavancin components.

11. The '061 Stogniew Patent describes lyophilized dalbavancin formulations at col. 22, line 54 to col. 31, line 54. The '061 Stogniew Patent also shows in Table 4 the results of stability studies carried out with these lyophilized compositions at different pH and temperature. Table 4 from the '061 Stogniew Patent, titled "Compositions of Various Dalbavancin Formulations", is reproduced below and includes 15 separate lyophilized dalbavancin compositions:

Table 4

Compositions of Various Dalbavancin Formulations

Composition	Dalbavancin (mg/vial)	Mannitol (mg/vial)	Lactose (mg/vial)	Ph
A	250	62.5	—	3.4
B	250	—	—	3.69
C	250	62.5	—	3.80
D	250	—	—	3.01
E	250	62.5	—	3.01
F	250	—	—	4.5
G	250	62.5	—	4.5
H	250	62.5	—	5.3
I	250	125	—	5.0
J	250	62.5	—	5.0
K	250	125	—	4.5
L	250	62.5	—	4.5
M	250	62.5	62.5	4.5
N	250	—	125	4.5
O	250	125	—	3.3

As explained in paragraphs 11-14 below, the lyophilized compositions in Table 4 of the '061 Stogniew Patent are prepared using dalbavancin prepared according to Example 11 of the '061 Stogniew Patent as the test API wherein said dalbavancin API has a pH of about 3.01. The stability of these lyophilized compositions was then investigated at temperatures from 25°C to 40°C for up to 6 months.

12. Methods for making the lyophilized composition in Table 4 of the '061 Stogniew Patent are generally described on col. 22, lines 5 to 53. First, dalbavancin API is prepared and isolated using a procedure such as that described Example 11 of the '061 Stogniew Patent (see col. 59, line 54 to col. 64, line 45). The dalbavancin API is then dissolved in water and formulated as described below:

A. In the case of Composition D, no other non-dalbavancin components (i.e., pH adjusting agent or stabilizer) are added, and the resultant solution (pH 3.01) is lyophilized.

B. In the case of Compositions B and F, the pH of each of the pre-lyophilate solutions is adjusted to increase (i.e., pH adjust) the pH to 3.69 (Composition B) and 4.5 (Composition F) prior to lyophilization.

C. Composition E is prepared by dissolving dalbavancin API in water followed by addition of mannitol; the resultant solution (pH 3.01) is then lyophilized.

D. The remaining compositions in Table 4 are prepared by dissolving dalbavancin API in water followed by addition of the indicated stabilizer(s); the pHs of the resultant solutions (3.01) are then adjusted and lyophilized.

13. The results of the stability studies are shown in Figures 1A through 4B and the accompanying tables of the '061 Stogniew Patent. The results show dalbavancin API tends to degrade with decreasing pH. For example, the '061 Stogniew Patent states at col. 23, lines 30 to 32, "dalbavancin composition D, which contains dalbavancin with no other non-dalbavancin components and which has not been pH adjusted (pH about 3.01)" contains a "significant amount (greater than 4%) of MAG" at Time=0.[1] In an analogous study, Composition B (similar to Composition D but pH adjusted to pH of 3.69 prior to lyophilization) contains 3.5 mol % MAG prior to any aging and/or heat treatment. Thus, the results of the stability study show that lyophilized dalbavancin compositions having a pH of less than about 3.7 and which contain no other non-dalbavancin components have a MAG content of at least about 3.5 mol % prior to any aging or heat treatment. I understand that this amount of MAG is more than the 3 mol % MAG that is required in the claims of the subject application.

14. I note the Examiner's statement on page 4 of the January 31, 2008 Office Action:

> "With respect to the composition disclosed by Malabarba et al. applicant has not made of record any evidence in verified form showing the pH of the composition disclosed by Malabarba et al. Further, applicant has not explained the statement in the U.S. Patent No. 7,119,061 that dalbavancin composition which has a pH of about 3.01 has not been pH adjusted."

15. I also note the statement at col. 20, lines 43-50 of the '061 Stogniew Patent which states

> a pharmaceutical composition is provided by dissolving a dried (e.g., lyophilized) dose of dalbavancin, often containing a stabilizer or mixture of stabilizers, in an amount of water and preferably deionized water in a volume sufficient for solubilization. Typically the amount of water sufficient for solubilization is approximately 10 ml, and the resulting pH of the dalbavancin solution is above 3.0, and about 3.5 to 4.5.

[1] The data (Figure 1B) show that Composition D contains 4.5% MAG prior to any aging and/or heat treatment.

16. In view of the above-cited sections of the '061 Stogniew Patent, I understand the statement in the '061 Stogniew Patent that Composition D "has not been pH adjusted" to mean that a 10 ml solution composed of 250 mg dalbavancin API (prepared and isolated according to Example 11 of the '061 Stogniew Patent) and water had a pH of 3.01; the solution was then lyophilized without any further adjustment of pH. The statement does not refer to pH adjustments that may have been carried out during the preparation and isolation of the dalbavancin API (such as those described in Example 11 of the '061 Stogniew Patent). In other words, adjustment of pH during preparation of the solution prior to lyophilization (as carried out, e.g., in the preparation of Compositions B and F of the '061 Stogniew Patent) is a separate endeavor from adjustment of dalbavancin API during the preparation and isolation of the API (as described in Example 11 of the '061 Stogniew Patent).

17. A method of making dalbavancin API is disclosed in the '509 Malabarba Patent in Example 10, col. 32, lines 20 to 38, and a method of purifying dalbavancin API using reverse-phase chromatography on silanized silica gel is disclosed in the '509 Malabarba Patent at col. 34, lines 39-61. Because the resin purification step described in the '509 Malabarba Patent is carried out in the presence of a mixture of acetonitrile and 0.1N acetic acid, I believe that the resultant dalbavancin API will have a pH of less than 7. In other words, dissolving 250 mg of dalbavancin API from Example 10 of the '509 Malabarba Patent in 10 ml of water (as described in the '061 Stogniew Patent at col. 20, lines 47-50 and Table 4) would produce an aqueous solution having a pH of less than 7. However, the '509 Malabarba Patent does not disclose the exact pH or the MAG content of its dalbavancin. Accepting the Examiner's reasoning that a dalbavancin composition prepared according to the '509 Malabarba Patent has a pH of about 3, I would expect a lyophilized composition containing such form of "dalbavancin with no other non-dalbavancin components and which has not been pH adjusted" to contain about 4.5 mol % MAG. I understand that this amount of MAG (4.5 mol %) exceeds the amount of MAG (3 mol %) amount that is claimed in the subject application.

18. As I noted above, I understand the claims of the subject application to cover a lyophilized dalbavancin pharmaceutical composition having a pH from about 3 to about 5, and including at least one stabilizer, wherein said stabilizer inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials. With regard to the "stabilizer," I note the statement at page 4, paragraph [0015] of the subject application which states:

> One or more stabilizing substances are employed to inhibit degradation of one or more dalbavancin components during storage as a dry powder (e.g., lyophilized) formulation and/or as an aqueous formulation prior to administration to an individual. Over time, degradation can result in the undesirable formation of less active and/or inactive components which could potentially cause adverse effects in vivo.

19. I also note the statement in the subject application at page 25, paragraph [0093]

> In some embodiments, pharmaceutical compositions of the invention include one or more stabilizing substances which inhibit degradation of one or more of the components of dalbavancin to less active or inactive materials, for example, MAG. As used herein, "stabilizing substance" or "stabilizer" refers to a substance that stabilizes the level of one or more of the constituent components of dalbavancin, for example, B_0, in the composition.

20. Based on the above statements in the subject application, I understand the term "stabilizer" as used in the claims of the subject application to mean a substance which inhibits chemical degradation of the one or more dalbavancin components. Those of ordinary skill in the art refer to such term as a *chemical stabilizer.*

21. As described in the subject application and the '061 Stogniew Patent, the degradation that occurs in low pH dalbavancin compositions can be inhibited by the addition of an suitable stabilizer, i.e., a chemical stabilizer. For example, Composition E in Table 4 (see paragraph 14 above) is prepared in the same manner and at the same pH as Composition D, except that Composition E is formulated with a stabilizer that inhibits degradation. Unlike Composition D (which results in 4.5 mol % MAG immediately following lyophilization, i.e., Time = 0), Composition E containing the stabilizer only results in 2.10 mol % MAG formation at Time=0. (See also Fig. 1B of the '061 Stogniew Patent.) Similarly, low pH Composition A (pH 3.4) which is formulated with a stabilizer initially forms 1.50 mol % MAG at Time=0, whereas Composition B, formulated at a higher pH (pH 3.69), initially forms 3.50 mol % MAG at Time=0. In summary, the data in Table 4 and other data in the '061 Stogniew Patent show that the degradation of dalbavancin API that occurs in acidic dalbavancin compositions (e.g., pH of about 5 or less) can be inhibited by including a suitable chemical stabilizer in the acidic formulations.

22. As discussed above, the '509 Malabarba Patent does not disclose any pharmaceutical composition containing dalbavancin API. In addition, I find no mention in the '509 Malabarba Patent relating to a lyophilized dalbavancin formulation at any pH, or that a lyophilized dalbavancin formulation should be chemically stabilized to prevent degradation to form non-dalbavancin components such as MAG. As described in the subject application and the '061 Stogniew Patent, a low pH lyophilized dalbavancin composition will degrade, e.g., form MAG, unless such lyophilized composition is formulated with a stabilizer that inhibits the formation of non-dalbavancin components.

23. I now refer to page 3 in the January 31, 2008 Office Action where the Examiner states:

> Malabarba et al. disclose dalbavancin (column 3). Malabarba et al. further disclose a composition comprising dalbavancin derivative and a stabilizer (column 28, lines 9-12) and disclose said composition in the form of a powder (column 28, line 13). Malabarba et al. further disclose the combination of dalbavancin derivative in combination with a sugar, such as lactose (column 27, lines 54-56).

The Examiner then states that the claimed invention is obvious in view of Malabarba because "it would have been prima facie obvious to a person having ordinary skill in the art at the time the claimed invention was made to combine dalbavancin with a stabilizer in order to produce a more stable composition."

24. I note first that the reference to "stabilizers" in the '509 Malabarba Patent is in the context of "formulary agents" useful for injectable compositions. As stated in the '509 Malabarba Patent at col. 28, lines 9-12: "Compositions for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. "

25. As described in the context of the '509 Malabarba Patent, I understand the term "suspending" agent to mean a component that reduces the agglomeration of particles in a dispersion to maintain a uniform suspension of solid particles in a liquid phase and increases viscosity; I understand the term "dispersing" agent to mean a component that aids or facilitates a uniform dispersion of finely divided solids in a liquid continuous phase; and I understand the term "stabilizing" agent to refer to a component useful for preventing formation of solids from a solution, preventing agglomeration of colloidal particles or maintaining the resuspendibility of coarse dispersions. Accordingly, I understand the term "formulatory agents" to refer to *physical stabilizers*, i.e., components whose purpose is to prevent phase separation or precipitate formation by colloids, or agglomeration of solid particles or emulsion particles in a liquid medium. I believe that the specific use of the terms "suspending, stabilizing and dispersing" in conjunction with the terms "suspension, solution, and emulsion" clearly relates to the *physical stability* pertaining to heterogeneous liquid dispersions. These terms have specific definitions and usage in the field of pharmaceutics and pharmaceutical formulation science.

26. In fundamental texts, such as Alfred Martin, Physical Pharmacy (4th ed. 1993) pages 477-494) (attached hereto as Exhibit A) and Remington: The Science and Practice of Pharmacy (A.R. Gennero ed., 19th ed. 1995) pages 278-291 and 1395 (attached hereto as Exhibit B), these terms are discussed relative to the prevention of coagulation, agglomeration and sedimentation due to physical forces, such as van Der Waals and electrostatic forces acting between colloidal or suspended particles. See for example pages 477-493 of Exhibit A and pages 278 to 291 of Exhibit B. I also note that in these texts the subject of *chemical stability* is addressed as a separate phenomenon and discussed in different chapters. Within the material presented in Exhibits A and B there is no ambiguity that the term "stabilizing" in the '509 Malabarba Patent refers to physical phenomena related to dispersions and is not making reference to inhibiting chemical reactions or alteration of chemical bonds within a molecule. The material in Exhibits A and B further indicates that the usage of terms relating to the word "stability", such as "stabilization", are contextual and that in the absence of specific clarification, their meaning is implied based upon the general category of the formulation system or phenomena under discussion. In the case of the '509 Malabarba Patent (col. 28, line 9-12) the context described is dispersions and therefore the term "stabilizer" refers to a

physical stabilizer. Based on my knowledge and experience and in view of the many technical treatises on pharmaceutical dispersions, I believe that the term "stability" as used in the context of the Malabarba '509 Patent is specifically, and exclusively, referring to aspects of *physical stabilization* of liquid dispersion. This is entirely different from chemical stabilization which is the object of the subject application. Also, the mechanism by which physical stabilizers function is based on different phenomena and therefore physical stabilizers used for liquid dispersion based formulations would not be useful or appropriate in providing chemical stabilization for a different type of formulation, i.e., a lyophile.

27. A second (and last) reference to compositions in the Malabarba '509 Patent relates to powder compositions. The '509 Malabarba Patent states at col. 28, lines 13-15: "Alternatively, the active ingredient may be in powder form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water." I note that no mention is made of using any "formulatory agents such as suspending, stabilizing and/or dispersing agents" with the dalbavancin powder of the Malabarba '509 Patent (in lines 13-15). As one skilled in the art, I note that the omission of such "formulatory agents" from a composition that solely consists of the "active ingredient in powder form" indicates that no formulatory agent (physical stabilizer) is required when the composition is in powder form. Such description of formulary agents to maintain physical stability as taught in the '509 Malabarba Patent would not lead me to make a dalbavancin composition containing a stabilizing agent that inhibits chemical degradation of dalbavancin into one or more non-dalbavancin components.

28. Lastly I note the Examiner's statement that "Malabarba et al further disclose the combination of dalbavancin derivative in combination with a sugar, such as lactose (col. 27, lines 54-56)." I note that the reference to "lactose" in the '509 Malabarba Patent is as a "diluent" for a "tablet" as stated at col. 27, line 54-55. The use of lactose as a diluent for an oral formulation such as a tablet is a completely separate endeavor from the use of a lactose as a stabilizer in a lyophilized dalbavancin pharmaceutical formulation that will be reconstituted and administered by injection or infusion I see nothing in the '509 Malabarba Patent that would suggest using "lactose" as a diluent in an injectable composition, let alone as a stabilizer as part of injectable composition or as part of a powder form for reconstitution as described at col. 28, lines 9-15 of the '509 Malabarba Patent.

29. In summary, the '509 Malabarba Patent provides only an extremely general description of pharmaceutical compositions. The '509 Malabarba Patent does not disclose the final pH of any dalbavancin pharmaceutical composition, and it makes no mention of the role of pH on dalbavancin stability as discussed in detail in the written description of the subject application and in the '061 Stogniew Patent. The general and limited discussion regarding pharmaceutical compositions described in the '509 Malabarba Patent provides no guidance to a pharmaceutical formulator to make or use a pharmaceutically acceptable and stable dalbavancin composition having a pH of from about 3 to about 5. Thus, the '509 Malabarba Patent provides no teaching or suggestion to one of ordinary skill in the art to formulate a stable

composition of dalbavancin API having a pH of about 3 to about 5 with a stabilizer that inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials, thereby resulting in a composition having a MAG content of less than about 3 mol %.

30. All statements made herein are of my own knowledge, are true and all statements made on information and belief are believed to be true. All statements made herein are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, in that willful false statements may jeopardize the validity the above-referenced application or any patent that may issue from it.

Date: 06 JUNE 2008

Paul Luner

Exhibit A

FOURTH EDITION

Physical Pharmacy

PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

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LEA & FEBIGER PHILADELPHIA, LONDON
1993

18
Coarse Dispersions

Particulate systems have been classified previously (Table 15–1, p. 394) on the basis of size into molecular dispersions (Chapter 5), colloidal systems (Chapter 15), and coarse dispersions (this chapter). The present discussion attempts to provide the pharmacist with an insight into the role of physics and chemistry in the research and development of the several classes of coarse dispersions. The theory and technology of these important pharmaceutical classes are based on interfacial and colloidal principles, micromeritics, and rheology. These topics have been introduced in the four previous chapters.

SUSPENSIONS

A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium. The particles have diameters for the most part greater than 0.1 μm, and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity.

Suspensions contribute to pharmacy and medicine by supplying insoluble and often distasteful substances in a form that is pleasant to the taste, by providing a suitable form for the application of dermatologic materials to the skin and sometimes to the mucous membranes, and for the parenteral administration of insoluble drugs. Therefore, pharmaceutical suspensions may be classified into three groups: orally administered mixtures, externally applied lotions, and injectable preparations.

Examples of oral suspensions are the oral antibiotic syrups, which normally contain 125 to 500 mg per 5 mL of solid material. When formulated for use as pediatric drops, the concentration of suspended material is correspondingly greater. Antacid and radioopaque suspensions generally contain high concentrations of dispersed solids. Externally applied suspensions for topical use are legion and are designed for dermatologic, cosmetic, and protective purposes. The concentration of dispersed phase may exceed 20%. Parenteral suspensions contain from 0.5 to 30% of solid particles. Viscosity and particle size are significant factors since they affect the ease of injection and the availability of the drug in depot therapy.

An acceptable suspension possesses certain desirable qualities, including the following. The suspended material should not settle rapidly; the particles that do settle to the bottom of the container must not form a hard cake but should be readily redispersed into a uniform mixture when the container is shaken; and the suspension must not be too viscous to pour freely from the orifice of the bottle or to flow through a syringe needle. In the case of an external lotion, the product must be fluid enough to spread easily over the affected area and yet must not be so mobile that it runs off the surface to which it is applied; the lotion must dry quickly and provide an elastic protective film that will not rub off easily; and it must have an acceptable color and odor.

It is important that the characteristics of the dispersed phase are chosen with care so as to produce a suspension having optimum physical, chemical, and pharmacologic properties. Particle size distribution, specific surface area, inhibition of crystal growth, and changes in polymorphic form are of special significance,

and the formulator must ensure that these and other properties[1-3] do not change sufficiently during storage to adversely affect the performance of the suspension. Finally, it is desirable that the product contain readily obtainable ingredients that can be incorporated into the mixture with relative ease by the use of standard methods and equipment.

The remainder of this section will be devoted to a discussion of some of the properties that provide the desirable characteristics just enumerated.

For pharmaceutical purposes, *physical stability* of suspensions may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion. Since this ideal situation is seldom realized, it is appropriate to add the statement that if the particles do settle, they should be easily resuspended by a moderate amount of agitation.

INTERFACIAL PROPERTIES OF SUSPENDED PARTICLES

Little is known about energy conditions at the surfaces of solids; yet a knowledge of the thermodynamic requirements is needed for the successful stabilization of suspended particles.

Work must be done to reduce a solid to small particles and disperse them in a continuous medium. The large surface area of the particles that results from the comminution is associated with a surface free energy that makes the system *thermodynamically unstable*, by which we mean that the particles are highly energetic and tend to regroup in such a way as to decrease the total area and reduce the surface free energy. The particles in a liquid suspension therefore tend to *flocculate*, that is, to form light, fluffy conglomerates that are held together by weak van der Waals forces. Under certain conditions—in a compacted cake, for example—the particles may adhere by stronger forces to form what are termed *aggregates*. Caking often occurs by the growth and fusing together of crystals in the precipitates to produce a solid aggregate.

The formation of any type of agglomerate, either floccules or aggregates, is taken as a measure of the system's tendency to reach a more thermodynamically stable state. An increase in the work W or surface free energy ΔG brought about by dividing the solid into smaller particles and consequently increasing the total surface area ΔA is given by

$$\Delta G = \gamma_{SL} \cdot \Delta A \qquad (18-1)$$

in which γ_{SL} is the interfacial tension between the liquid medium and the solid particles.

Example 18–1. Compute the change in the surface free energy of a solid in a suspension if the total surface is increased from 10^3 cm^2 to 10^7 cm^2. Assume that the interfacial tension between the solid and the liquid medium is $\gamma_{LS} = 100$ dyne/cm.

The initial free energy is

$$G_1 = 100 \times 10^3 = 10^5 \text{ erg/cm}^2$$

When the surface area is 10^7 cm^2,

$$G_2 = 100 \times 10^7 = 10^9 \text{ erg/cm}^2$$

The change in the free energy, ΔG_{21}, is $10^9 - 10^5 \simeq 10^9$ erg/cm^2. The free energy has been increased by 10^9, which makes the system more thermodynamically unstable.

In order to approach a stable state, the system tends to reduce the surface free energy; equilibrium is reached when $\Delta G = 0$. This condition may be accomplished, as seen from equation (18–1), by a reduction of interfacial tension, or it may be approached by a decrease of the interfacial area. The latter possibility, leading to flocculation or aggregation, may be desirable or undesirable in a pharmaceutical suspension, as considered in a later section.

The interfacial tension can be reduced by the addition of a surfactant but cannot ordinarily be made equal to zero. A suspension of insoluble particles, then, usually possesses a finite positive interfacial tension, and the particles tend to flocculate. An analysis paralleling this one could also be made in the breaking of an emulsion.

The forces at the surface of a particle affect the degree of flocculation and agglomeration in a suspension. Forces of attraction are of the London–van der Waals type; the repulsive forces arise from the interaction of the electric double layers surrounding each particle. The formation of the electric double layer has been considered in detail in Chapter 14, which dealt with interfacial phenomena. The student is advised to review, at this point, the section dealing with the electrical properties of interfaces (pp. 386–388) since particle charge, electrical double layer formation, and zeta potential are all relevant to the present topic.

The potential energy of two particles is plotted in Figure 18–1 as a function of the distance of separation. Shown are the curves depicting the energy of attraction, the energy of repulsion, and the net energy, which has a peak and two minima. When the repulsion energy is high, the potential barrier is also high, and collision of the particles is opposed. The system remains deflocculated, and, when sedimentation is complete, the particles form a close-packed arrangement with the smaller particles filling the voids between the larger ones. Those particles lowest in the sediment are gradually pressed together by the weight of the ones above; the energy barrier is thus overcome, allowing the particles to come into close contact with each other. In order to resuspend and redisperse these particles, it is again necessary to overcome the high energy barrier. Since this is not easily achieved by agitation, the particles tend to remain strongly attracted to each other and form a hard cake. When the particles are flocculated, the energy barrier is still too large to be surmounted, and so the approaching particle resides in the second energy minimum, which is at a distance of separation of perhaps 1000 to 2000 Å. This distance is sufficient to

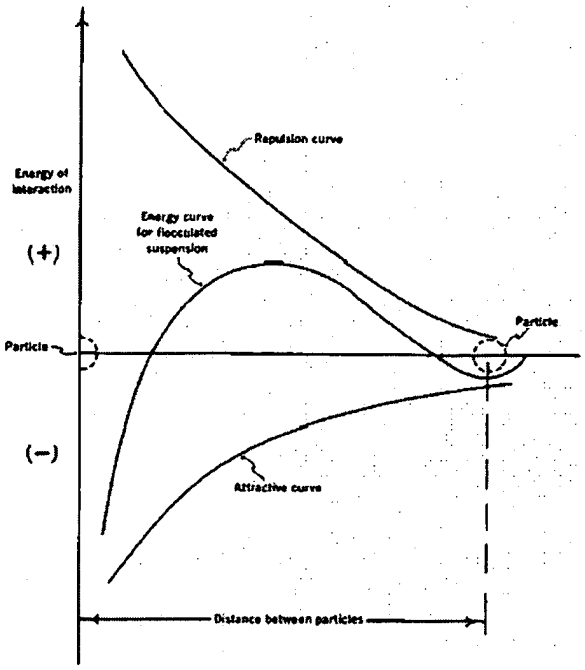

Fig. 18–1. Potential energy curves for particle interactions in suspension (from A. Martin, J. Pharm. Sci., 50, 514, 1961, reproduced with permission of the copyright owner.)

form the loosely structural flocs. These concepts evolve from the DLVO theory for the stability of lyophobic sols (p. 408). Schneider et al.[4] prepared a computer program to calculate the repulsion and attraction energies in pharmaceutical suspensions. They showed the methods of handling the DLVO equations, and the careful consideration that must be given to the many physical units involved. Detailed examples of calculations were given.

To summarize, flocculated particles are weakly bonded, settle rapidly, do not form a cake, and are easily resuspended; deflocculated particles settle slowly and eventually form a sediment in which aggregation occurs with the resultant formation of a hard cake that is difficult to resuspend.

SETTLING IN SUSPENSIONS

As mentioned earlier, one aspect of physical stability in pharmaceutical suspensions is concerned with keeping the particles uniformly distributed throughout the dispersion. Although it is seldom possible to prevent settling completely over a prolonged period of time, it is necessary to consider the factors that influence the velocity of sedimentation.

Theory of Sedimentation. As discussed in Chapter 16, the velocity of sedimentation is expressed by Stokes' law:

$$v = \frac{d^2(\rho_s - \rho_o)g}{18\eta_o} \qquad (18\text{–}2)$$

in which v is the terminal velocity in cm/sec, d is the diameter of the particle in cm, ρ_s and ρ_o are the densities of the dispersed phase and dispersion medium, respectively, g is the acceleration due to gravity, and η_o is the viscosity of the dispersion medium in poise.

Dilute pharmaceutical suspensions containing less than about 2 g of solids per 100 mL of liquid conform roughly to these conditions. (Some workers feel that the concentration must be less than 0.5 g/100 mL before Stokes' equation is valid.) In dilute suspensions, the particles do not interfere with one another during sedimentation, and *free settling* occurs. In most pharmaceutical suspensions that contain dispersed particles in concentrations of 5%, 10%, or higher percentages, the particles exhibit *hindered settling*. The particles interfere with one another as they fall, and Stokes' law no longer applies.

Under these circumstances, some estimation of physical stability may be obtained by diluting the suspension so that it contains about 0.5 to 2.0% *w/v* of dispersed phase. This is not always recommended, however, because the stability picture obtained is not necessarily that of the original suspension. The addition of a diluent may affect the degree of flocculation (or deflocculation) of the system, thereby effectively changing the particle size distribution.

To account for the nonuniformity in particle shape and size invariably encountered in real systems. Stokes' equation may be written in other forms. One of the proposed modifications is as follows:[5]

$$v' = v\epsilon^n \qquad (18\text{–}3)$$

where v' is the rate of fall at the interface in cm/sec and v is the velocity of sedimentation according to Stokes' law. The term ϵ represents the initial porosity of the system, that is, the initial volume fraction of the uniformly mixed suspension, which varies from zero to unity. The exponent n is a measure of the "hindering" of the system. It is a constant for each system.

Example 18–2. The average particle diameter of calcium carbonate in aqueous suspension is 54 μm. The densities of $CaCO_3$ and water, respectively, are 2.7 and 0.997 g/cm³. The viscosity of water is 0.009 poise at 25° C. Compute the rate of fall v' for $CaCO_3$ samples at two different porosities, $\epsilon_1 = 0.95$ and $\epsilon_2 = 0.5$. The n value is 19.73.

From Stokes' law (equation (18–2)),

$$v = \frac{(54 \times 10^{-4})^2(2.7 - 0.997)981}{18 \times 0.009} = 0.30 \text{ cm/sec}$$

Taking logarithms on both sides of equation (18–3), $\ln v' = \ln v + n \ln \epsilon$.

For $\epsilon_1 = 0.95$,

$$\ln v' = -1.204 + [19.73(-0.051)] = -2.210$$

$$v' = 0.11 \text{ cm/sec}$$

Analogously, for $\epsilon_2 = 0.5$, $v' = 3.5 \times 10^{-7}$ cm/sec. Note that at low porosity values (i.e., 0.5, which corresponds to a high concentration of solid in suspension), the sedimentation is hindered, leading to small v'

values. On the other hand, when the suspension becomes infinitely diluted (i.e., $\epsilon = 1$), the rate of fall $v' = v$. In the present example, if $\epsilon = 1$,

$$v' = 0.3 \times 1^{19.73} = 0.3 \text{ cm/sec}$$

which is the Stokes' law velocity.

Effect of Brownian Movement. For particles having a diameter of about 2 to 5 μm (depending on the density of the particles and the density and viscosity of the suspending medium), Brownian movement counteracts sedimentation to a measurable extent at room temperature by keeping the dispersed material in random motion. The *critical radius* r below which particles will be kept in suspension by kinetic bombardment of the particles by the molecules of the suspending medium (Brownian movement) has been worked out by Burton.[6]

It may be seen in the microscope that Brownian movement of the smallest particles in a field of particles of a pharmaceutical suspension is usually eliminated when the sample is dispersed in a 50% glycerin solution, having a viscosity of about 5 cps. Hence, it is unlikely that the particles in an ordinary pharmaceutical suspension, containing suspending agents, are in a state of vigorous Brownian motion.

Sedimentation of Flocculated Particles. When sedimentation is studied in flocculated systems, it is observed that the flocs tend to fall together, producing a distinct boundary between the sediment and the supernatant liquid. The liquid above the sediment is clear because even the small particles present in the system are associated with the flocs. Such is not the case in deflocculated suspensions having a range of particle sizes, in which, in accordance with Stokes' law, the larger particles settle more rapidly than the smaller particles. No clear boundary is formed (unless only one size particle is present), and the supernatant remains turbid for a considerably longer period of time. Whether or not the supernatant liquid is clear or turbid during the initial stages of settling is a good indication of whether the system is flocculated or deflocculated, respectively.

According to Hiestand,[7] the initial rate of settling of flocculated particles is determined by the floc size and the porosity of the aggregated mass. Subsequently, the rate depends on compaction and rearrangement processes within the sediment. The term *subsidence* is sometimes used to describe settling in flocculated systems.

Sedimentation Parameters. Two useful parameters that may be derived from sedimentation (or more correctly, subsidence) studies are *sedimentation volume*, V, or *height*, H, and *degree of flocculation*.

The sedimentation volume, F, is defined as the ratio of the final, or ultimate, volume of the sediment, V_u, to the original volume of the suspension, V_o, before settling. Thus

$$F = V_u/V_o \qquad (18\text{–}4)$$

The sedimentation volume can have values ranging from less than 1 to greater than 1. F is normally less than 1, and in this case, the ultimate volume of sediment is smaller than the original volume of suspension, as shown in Figure 18–2*a*, in which $F = 0.5$. If the volume of sediment in a flocculated suspension equals the original volume of suspension, then $F = 1$ (Fig. 18–2*b*). Such a product is said to be in "flocculation equilibrium" and shows no clear supernatant on standing. It is therefore pharmaceutically acceptable. It is possible for F to have values greater than 1, meaning that the final volume of sediment is greater than the original suspension volume. This comes about because the network of flocs formed in the suspension are so loose and fluffy that the volume they are able to encompass is greater than the original volume of

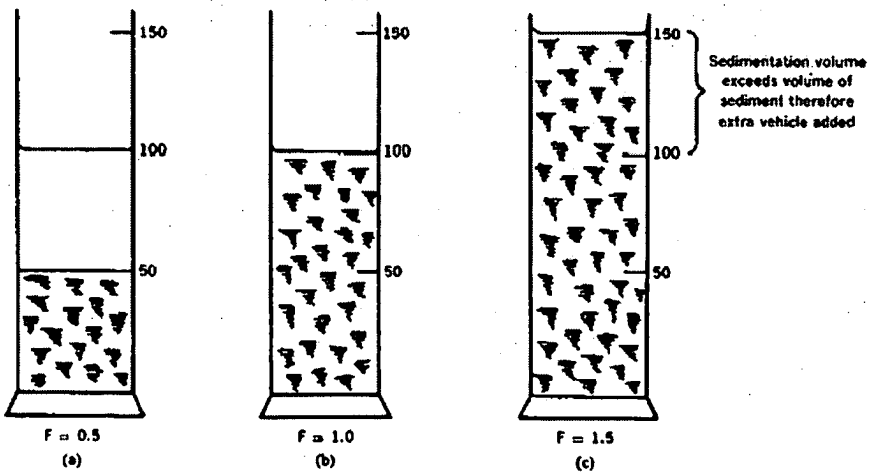

Fig. 18–2. Sedimentation volumes produced by adding varying amounts of flocculating agent. Examples *(b)* and *(c)* are pharmaceutically acceptable.

suspension. This situation is illustrated in Figure 18–2c, in which sufficient extra vehicles has been added to contain the sediment. In example shown, $F = 1.5$.

The sedimentation volume gives only a qualitative account of flocculation since it lacks a meaningful reference point.[7] A more useful parameter for flocculation is β, the *degree of flocculation*.

If we consider a suspension that is completely deflocculated, the ultimate volume of the sediment will be relatively small. Writing this volume as V_∞, based on equation (18–4), we have

$$F_\infty = V_\infty/V_0 \qquad (18\text{–}5)$$

in which F_∞ is the sedimentation volume of the deflocculated, or peptized, suspension. The degree of flocculation, β, is therefore defined as the ratio of F to F_∞, or

$$\beta = F/F_\infty \qquad (18\text{–}6)$$

Substituting equations (18–4) and (18–5) in equation (18–6), we obtain

$$\beta = \frac{V_u/V_0}{V_\infty/V_0} = V_u/V_\infty \qquad (18\text{–}7)$$

The degree of flocculation is a more fundamental parameter than F since it relates the volume of flocculated sediment to that in a deflocculated system. We can therefore say that

$$\beta = \frac{\text{ultimate sediment volume of } \textit{flocculated} \text{ suspension}}{\text{ultimate sediment volume of } \textit{deflocculated} \text{ suspension}}$$

Example 18–3. Compute the sedimentation volume of a 5% (*w/v*) suspension of magnesium carbonate in water. The initial volume is $V_0 = 100$ mL and the final volume of the sediment is $V_u = 30$ mL. If the degree of flocculation is $\beta = F/F_\infty = 1.3$, what is the deflocculated sedimentation volume, F_∞

$$F = \frac{30}{100} = 0.30$$

$$F_\infty = F/\beta = 0.30/1.3 = 0.23$$

FORMULATION OF SUSPENSIONS

The approaches commonly used in the preparation of physical stable suspensions fall into two categories—the use of structured vehicle to maintain deflocculated particles in suspension, and the application of the principles of flocculation to produce flocs that, although they settle rapidly, are easily resuspended with a minimum of agitation.

Structured vehicles are pseudoplastic and plastic in nature; their rheologic properties have been discussed in Chapter 17. As we shall see in a later section, it is frequently desirable that thixotropy be associated with these two types of flow. Structured vehicles act by entrapping the particles (generally deflocculated) so that, ideally, no settling occurs. In reality, some degree of sedimentation will usually take place. The "shear-thinning" property of these vehicles does, however, facilitate the reformation of a uniform dispersion when shear is applied.

A disadvantage of deflocculated systems, mentioned earlier, is the formation of a compact cake when the particles eventually settle. It is for this reason that the formulation of flocculated suspensions has been advocated.[8] Optimum physical stability and appearance will be obtained when the suspension is formulated with flocculated particles in a structured vehicle of the hydrophilic colloid type. Consequently, most of the subsequent discussion will be concerned with this approach and the means by which controlled flocculation may be achieved. Whatever approach is used, the product must (1) flow readily from the container and (2) possess a uniform distribution of particles in each dose.

Wetting of Particles. The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process and requires further consideration. Powders sometimes are added to the vehicle, particularly in large-scale operations, by dusting on the surface of the liquid. It is frequently difficult to disperse the powder owing to an adsorbed layer of air, minute quantities of grease, and other contaminants. The powder is not readily wetted, and although it may have a high density, it floats on the surface of the liquid. Finely powdered substances are particularly susceptible to this effect because of entrained air, and they fail to become wetted even when forced below the surface of the suspending medium. The *wettability* of a powder may be ascertained easily by observing the contact angle (p. 384) that powder makes with the surface of the liquid. The angle is approximately 90° when the particles are floating well out of the liquid. A powder that floats low in the liquid has a lesser angle, and one that sinks obviously shows no contact angle. Powders that are not easily wetted by water and accordingly show a large contact angle, such as sulfur, charcoal, and magnesium stearate, are said to be *hydrophobic*. Powders that are readily wetted by water when free of adsorbed contaminants are called *hydrophilic*. Zinc oxide, talc, and magnesium carbonate belong to the latter class.

Surfactants are quite useful in the preparation of a suspension in reducing the interfacial tension between solid particles and a vehicle. As a result of the lowered interfacial tension, the advancing contact angle is lowered, air is displaced from the surface of particles, and wetting and deflocculation are promoted. Schott et al.[9] studied the deflocculating effect of octoxynol, a nonionic surfactant, to enhance the dissolution rate of prednisolone from tablets. The tablets break up into fine granules that are deflocculated in suspension. The deflocculating effect is proportional to the surfactant concentration. However, at very high surfactant concentration, say, 15 times the critical micelle concentra-

tion, the surfactant produces extensive flocculation. Glycerin and similar hygroscopic substances are also valuable in levigating the insoluble material. Apparently, glycerin flows into the voids between the particles to displace the air and, during the mixing operation, coats and separates the material so that water can penetrate and wet the individual particles. The dispersion of particles of colloidal gums by alcohol, glycerin, and propylene glycol, allowing water to subsequently penetrate the interstices, is a well-known practice in pharmacy.

To select suitable wetting agents that possess a well-developed ability to penetrate the powder mass, Hiestand[7] has used a narrow trough, several inches long and made of a hydrophobic material, such as Teflon, or coated with paraffin wax. At one end of the trough is placed the powder and at the other end the solution of the wetting agent. The rate of penetration of the latter into the powder can then be observed directly.

Controlled Flocculation. Assuming that the powder is properly wetted and dispersed, attention may now be given to the various means by which controlled flocculation may be produced so as to prevent formation of a compact sediment that is difficult to redisperse. The topic, described in detail by Hiestand,[7] is conveniently discussed in terms of the material used to produce flocculation in suspensions, namely electrolytes, surfactants, and polymers.

Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta potential and the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

If we disperse particles of bismuth subnitrate in water, we find that, based on electrophoretic mobility studies, they possess a large positive charge, or zeta potential. Because of the strong forces of repulsion between adjacent particles, the system is peptized or deflocculated. By preparing a series of bismuth subnitrate suspensions containing increasing concentrations of monobasic potassium phosphate, Haines and Martin[10] were able to show a correlation between apparent zeta potential and sedimentation volume, caking, and flocculation. The results are summarized in Figure 18–3 and are explained in the following manner.

The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of the negatively charged phosphate anion. With the continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in a negative direction, as shown in Figure 18–3. Microscopic examination of the various suspensions shows that at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again. The onset of flocculation coincides with the maximum sedimentation volume determined. F remains reasonably constant while floc-

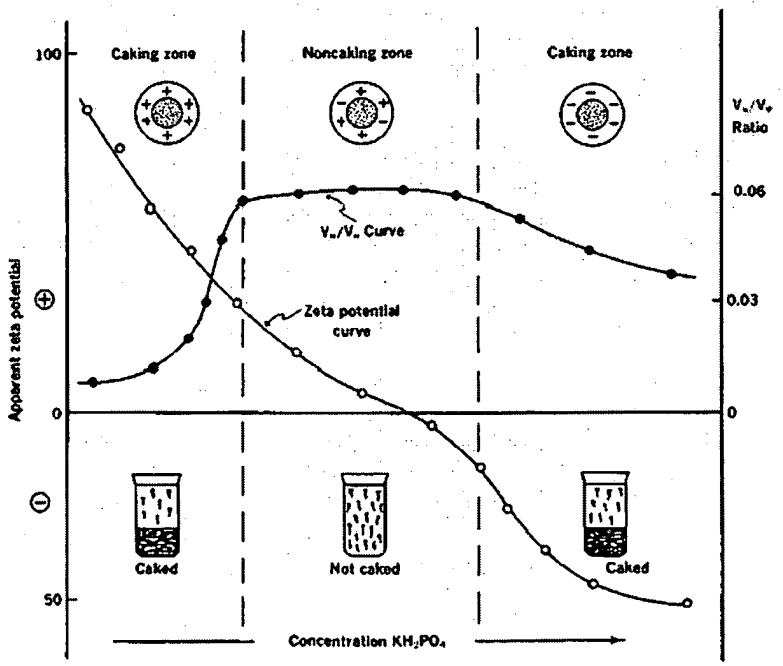

Fig. 18–3. Caking diagram, showing the flocculation of a bismuth subnitrate suspension by means of the flocculating agent, monobasic potassium phosphate. (From A. Martin and J. Swarbrick, in Sprowls, *American Pharmacy*, 6th Edition, Lippincott, Philadelphia, 1966, p. 205, reproduced with permission of the copyright owner.)

culation persists, and only when the zeta potential becomes sufficiently negative to effect repeptization does the sedimentation volume start to fall. Finally, the absence of caking in the suspensions correlates with the maximum sedimentation volume, which, as stated previously, reflects the amount of flocculation. At less than maximum values of F, caking becomes apparent.

These workers[10] also demonstrated a similar correlation when aluminum chloride was added to a suspension of sulfamerazine in water. In this system, the initial zeta potential of the sulfamerazine particles is negative and is progressively reduced by adsorption of the trivalent aluminum cation. When sufficient electrolyte is added, the zeta potential reaches zero and then increases in a positive direction. Colloidal and coarse dispersed particles may possess surface charges that depend on the pH of the system. An important property of the pH-dependent dispersions is the zero point of charge, that is, the pH at which the net surface charge is zero. The desired surface charge can be achieved through adjusting the pH by the addition of HCl or NaOH to produce a positive, zero, or negative surface charge. The negative zeta potential of nitrofurantoin decreases considerably when the pH values of the suspension are charged from basic to acidic.[11]

Surfactants, both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical since these compounds may also act as wetting and deflocculating agents to achieve dispersion.

Polymers are long-chain, high-molecular-weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.

Felmeister and others[12] studied the influence of a xanthan gum (an anionic heteropolysaccharide) on the flocculation characteristics of sulfaguanidine, bismuth subcarbonate, and other drugs in suspension. Addition of xanthan gum resulted in increased sedimentation volume, presumably by a polymer bridging phenomenon. Hiestand[13] has reviewed the control of floc structure in coarse suspensions by the addition of polymeric materials.

Hydrophilic polymers also act as protective colloids (p. 410), and particles coated in this manner are less prone to cake than are uncoated particles. These polymers exhibit pseudoplastic flow in solution, and this property serves to promote physical stability within the suspension. Gelatin, a polyelectrolytic polymer, exhibits flocculation that depends on the pH and ionic strength of the dispersion medium. Sodium sulfathiazole, precipitated from acid solution in the presence of gelatin, was shown by Blythe[14] to be free flowing in the dry state and not to cake when suspended. Sulfathiazole normally carries a negative charge in aqueous vehicles. The coated material, precipitated from acid solution in the presence of gelatin, however, was found to carry a positive charge. This is due to gelatin being positively charged at the pH at which precipitation was carried out. It has been suggested[8] that the improved properties result from the positively charged gelatin-coated particles being partially flocculated in suspension, presumably because the high negative charge has been replaced by a smaller, albeit positive, charge. Positively charged liposomes have been used as flocculating agents to prevent caking of negatively charged particles. Liposomes are vesicles of phospholipids having no toxicity and that can be prepared in various particle sizes.[15] They are adsorbed on the negatively charged particles. (See page 513 for a discussion of liposomes.)

Flocculation in Structured Vehicles. Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close, or equal, to 1. Consequently, in practice, a suspending agent is frequently added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth, or bentonite have been employed, either alone or in combination.

This may lead to incompatibilities, depending on the initial particle charge and the charge carried by the flocculating agent and the suspending agent. For example, suppose we prepare a dispersion of positively charged particles that is then flocculated by the addition of the correct concentration of an anionic electrolyte such as monobasic potassium phosphate. We can improve the physical stability of this system by adding a minimal amount of one of the hydrocolloids mentioned above. No physical incompatibility will be observed because the majority of hydrophilic colloids are themselves negatively charged and are thus compatible with anionic flocculating agents. If, however, we flocculate a suspension of negatively charged particles with a cationic electrolyte (aluminum chloride), the subsequent addition of a hydrocolloid may result in an incompatible product, as evidenced for the formation of an unsightly stringy mass that has little or no suspending action and itself settles rapidly.

Under these circumstances, it becomes necessary to use a protective colloid to change the sign on the particle from negative to positive. This is achieved by the adsorption onto the particle surface of a fatty acid amine (which has been checked to ensure its nontoxicity) or a material such as gelatin, which is positively charged below its isoelectric point. We are then able to use an anionic electrolyte to produce flocs that are compatible with the negatively charged suspending agent.

The student should note that this approach may be used regardless of the charge on the particle. The

sequence of events is depicted in Figure 18–4, which is self-explanatory.

Rheologic Considerations. The principles of rheology may be applied to a study of the following factors: the viscosity of a suspension as it affects the settling of dispersed particles, the change in flow properties of the suspension when the container is shaken and when the product is poured from the bottle, and the spreading qualities of the lotion when it is applied to an affected area. Rheologic considerations are also important in the manufacture of suspensions.

The only shear that occurs in a suspension in storage is due to a settling of the suspended particles; this force is negligible and may be disregarded. When the container is shaken and the product is poured from the bottle, however, a high shearing rate is manifested. As suggested by Mervine and Chase,[16] the ideal suspending agent should have a *high* viscosity at negligible shear, that is, during shelf storage; and it should have a *low* viscosity at high shearing rates, that is, it should be free-flowing during agitation, pouring, and spreading. As seen in Figure 18–5, pseudoplastic substances such as tragacanth, sodium alginate, and sodium carboxymethylcellulose show these desirable qualities. The Newtonian liquid, glycerin, is included in the graph for comparison. Its viscosity is suitable for suspending particles but is too high to pour easily and to spread on the skin. Furthermore, glycerin shows the undesirable property of tackiness (stickiness) and is too hygroscopic to use in undiluted form. The curves in Figure 18–5 were obtained by use of the modified Stormer viscometer described on page 464.

A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful since it forms a gel on standing and becomes fluid when disturbed.

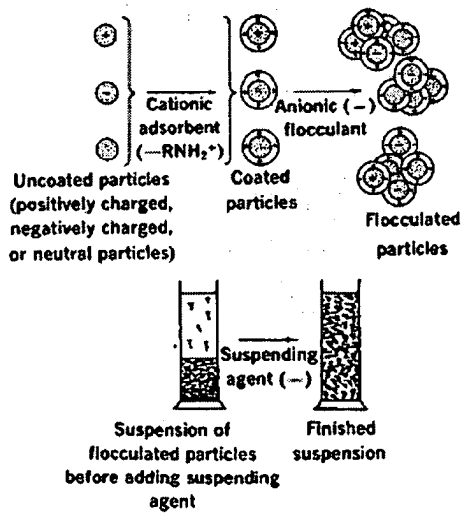

Fig. 18–4. The sequence of steps involved in the formation of a stable suspension (From A. Martin and J. Swarbrick; in Sprowls, *American Pharmacy*, 6th Edition, Lippincott, Philadelphia, 1966, p. 206, reproduced with permission of the copyright owner.)

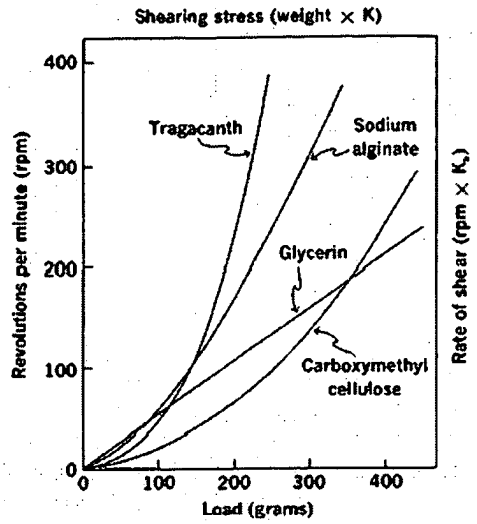

Fig. 18–5. Rheologic flow curves of various suspending agents analyzed in a modified Stormer viscometer.

Figure 18–6 shows the consistency curves for bentonite, Veegum (Vanderbilt Co.), and a combination of bentonite and sodium carboxymethylcellulose (CMC). The hysteresis loop of bentonite is quite marked. Veegum also shows considerable thixotropy, both when tested by inverting a vessel containing the dispersion and when analyzed in a rotational viscometer. When bentonite and CMC dispersions are mixed, the resulting curve shows both pseudoplastic and thixotropic characteristics. Such a combination should produce an excellent suspending medium.

Preparation of Suspensions. The factors entering into the preparation and stabilization of suspensions involve certain principles of interest to physical pharmacy and are briefly discussed here. The physical principles involved in the dispersion of solids by different types of equipment have been discussed by Oldshue.[17]

A suspension is prepared on the small scale by grinding or levigating the insoluble material in the

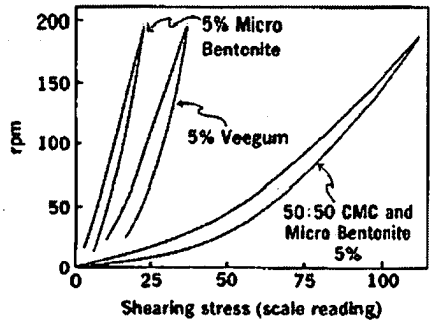

Fig. 18–6. Flow curves for 5% suspending agents in water showing thixotropy. The curves were obtained with the Ferranti-Shirley cone-plate viscometer.

mortar to a smooth paste with a vehicle containing the dispersion stabilizer and gradually adding the remainder of the liquid phase in which any soluble drugs may be dissolved. The slurry is transferred to a graduate, the mortar is rinsed with successive portions of the vehicle, and the dispersion is finally brought to the final volume.

On a large scale, dispersion of solids in liquids is accomplished by the use of ball, pebble, and colloid mills. Dough mixers, pony mixers, and similar apparatus are also employed. Only the colloid mill is described here; a discussion of the other mills can be found in the book by Fischer.[18] Dry grinding in ball mills is treated by Fischer, by Berry and Kamack and by Prasher.[18]

The colloid mill is based on the principle of a high-velocity cone-shaped rotor that is centered with respect to a stator at a small adjustable clearance. The suspension is fed to the rotor by gravity through a hopper, sheared between the rotor and stator, and forced out below the stator, where it may be recycled or drawn off.

The efficiency of the mill is based on the clearance between the disks, the peripheral velocity of the rotor, and the non-Newtonian viscosity of the suspension. The mill breaks down the large aggregates and flocs so that they may be dispersed throughout the liquid vehicle and then protected by the dispersion stabilizer. The shearing action that leads to disaggregation occurs at the surfaces of the rotating and stationary disks, and between the particles themselves in a concentrated suspension. If the yield value is too great, the material fails to flow; if the viscosity is low, a loss in effectiveness of shearing action occurs. Therefore, the yield value should be low, and the plastic or apparent viscosity of the material should be at a maximum consistent with the optimum rate of flow through the mill. If the material is highly viscous or if the plates are adjusted to a clearance that is too narrow, the temperature rises rapidly, and cooling water must be circulated around the stator to dissipate the heat that is produced. Dilatant materials—for example, deflocculated suspensions containing 50% or more of solids—are particularly troublesome. They flow freely into the mill but set up a high shearing rate and produce overheating and stalling of the motor. Beginning any milling process with the plates set at a wide clearance minimizes this danger. If this technique fails, however, the material must be milled in another type of equipment or the paste must be diluted with a vehicle until dilatancy is eliminated.

Physical Stability of Suspensions. Raising the temperature often leads to flocculation of *sterically stabilized* suspensions, that is, suspensions stabilized by nonionic surfactants. Repulsion due to steric interactions depends on the nature, thickness, and completeness of the surfactant-adsorbed layers on the particles. When the suspension is heated the energy of repulsion between the particles may be reduced owing to dehydration of the polyoxyethylene groups of the surfactant. The attractive energy is increased and the particles flocculate.[19] Zapata et al.[20] studied the mechanism of freeze–thaw instability in aluminum hydrocarbonate and magnesium hydroxide gels as model suspensions because of their well known sensitivity to temperature changes. During the freezing process, particles are able to overcome the repulsive barrier caused by ice formation, which forces the particles close enough to experience the strong attractive forces present in the primary minimum, and form aggregates according to the DLVO theory (see Fig. 15–12, p. 409). When the ice melts, the particles remain as aggregates unless work is applied to overcome the primary energy peak. Aggregate size was found to be inversely related to the freezing rate: the higher the freezing rate, the smaller the size of ice crystals formed. These small crystals do not result in the aggregation of as many suspension particles as do large ice crystals.

In addition to particle aggregation, particle growth is also a destabilizing process resulting from temperature fluctuations or *Ostwald ripening* during storage. Fluctuations of temperature may change the particle size distribution and polymorphic form of a drug, altering the absorption rate and drug bioavailability.[21] Particle growth is particularly important when the solubility of the drug is strongly dependent on the temperature. Thus, when temperature is raised, crystals of drug may dissolve and form supersaturated solutions, which favor crystal growth. This can be prevented by the addition of polymers or surfactants. Simonelli et al.[22] studied the inhibition of sulfathiazole crystal growth by polyvinylpyrrolidone. These authors suggested that the polymer forms a noncondensed netlike film over the sulfathiazole crystal, allowing the crystal to grow out only through the openings of the net. The growth is thus controlled by the pore size of the polymer network at the crystal surface. The smaller the pore size, the higher the supersaturation of the solution required for the crystals to grow. This can be shown using the Kelvin equation (p. 440), as applied to a particle suspended in a saturated solution:[22]

$$\ln \frac{c}{c_0} = \frac{2\gamma M}{NkT\rho R} \qquad (18\text{–}8)$$

where c is the solubility of a small particle of radius R in an aqueous vehicle and c_0 the solubility of a very large crystalline particle; γ is the interfacial tension of the crystal, ρ is the density of the crystal, and M is the molecular weight of the solute. N is Avogadro's number, k is the Boltzmann constant and $N \times k = 8.314 \times 10^7$ erg deg^{-1} mole^{-1}. The ratio c/c_0 defines the supersaturation ratio that a large crystal requires in the aqueous solution saturated with respect to the small particle. According to equation (18–8), as the radius of curvature of a protruding crystal decreases, the protrusion will require a correspondingly larger supersaturation ratio before it can grow. The radius of curvature of

a protrusion must equal that of the pore of the polymer on the crystal surface.

Example 18–4. Assume that the interfacial tension of a particle of drug in an aqueous vehicle is 100 erg/cm^2, its molecular weight 200 g/mole, and the temperature of solution 30° C or 303° K. (*a*) Compute the supersaturation ratio c/c_o that is required for the crystal to grow. The radius R of the particle is 5 μm or 5×10^{-4} cm and its density is 1.3 g/cm^3. (*b*) Compute the supersaturation ratio when the particle is covered by a polymer and the pore radius R of the polymer at the crystal surface is 6×10^{-7} cm.

Using the Kelvin equation,

(*a*)

$$\ln \frac{c}{c_o} = \frac{2 \times 100 \times 200}{8.314 \times 10^7 \times 1.3 \times 303 \times 5 \times 10^{-4}} = 0.0024$$

$$c/c_o = \text{antiln}(0.0024) = 1.002$$

(*b*)

$$\ln \frac{c}{c_o} = \frac{2 \times 100 \times 200}{8.314 \times 10^7 \times 1.3 \times 303 \times 6 \times 10^{-7}} = 2.036$$

$$c/c_o = \text{antiln}(2.036) = 7.66$$

Notice that c/c_o *in part (a)* represents slight oversaturation whereas in (*b*) the supersaturation concentration must be 7.6 times larger than the solubility of the drug molecule for the crystalline particle to grow. In other words, the addition of a polymer greatly increases the point at which supersaturation occurs and makes it more difficult for the drug crystal to grow.

Ziller and Rupprecht[23] designed a control unit to monitor crystal growth and studied the inhibition of growth by PVP in acetaminophen suspensions. According to these workers, some of the segments of the polymer PVP attach to the free spaces on the drug crystal lattice and the polymer is surrounded by a hydration shell (Fig. 18–7). The adsorbed segments of the polymer inhibit crystal growth of acetaminophen because they form a barrier that impedes the approach of the drug molecules from the solution to the crystal surface. High-molecular-weight polymers of PVP are more effective than low-molecular-weight polymers since the adsorption of the polymer on the crystal surface becomes more irreversible as the chain length increases.

The stability of suspensions may also decrease owing to interaction with excipients dissolved in the dispersion medium. Zatz and Lue[19] studied the flocculation by sorbitol in sulfamerazine suspensions containing nonionic surfactants as wetting agents. The flocculation by sorbitol depends on the cloud point of the surfactant. Thus, the lower the cloud point, the less sorbitol was needed to induce flocculation. The fact that the cloud point can be lowered by preservatives such as methylparaben shows that the choice of additives may change the resistance to caking of a suspension containing nonionic surfactants. Zatz and Lue[19] suggested that the cloud point may be used to estimate the critical flocculation concentration of sorbitol. Lucks et al.[24] studied the adsorption of preservatives such as cetylpyridinium chloride on zinc oxide particles in suspension. Increasing amounts of this preservative led to charge reversal of the suspension. Cetylpyridinium chloride, a

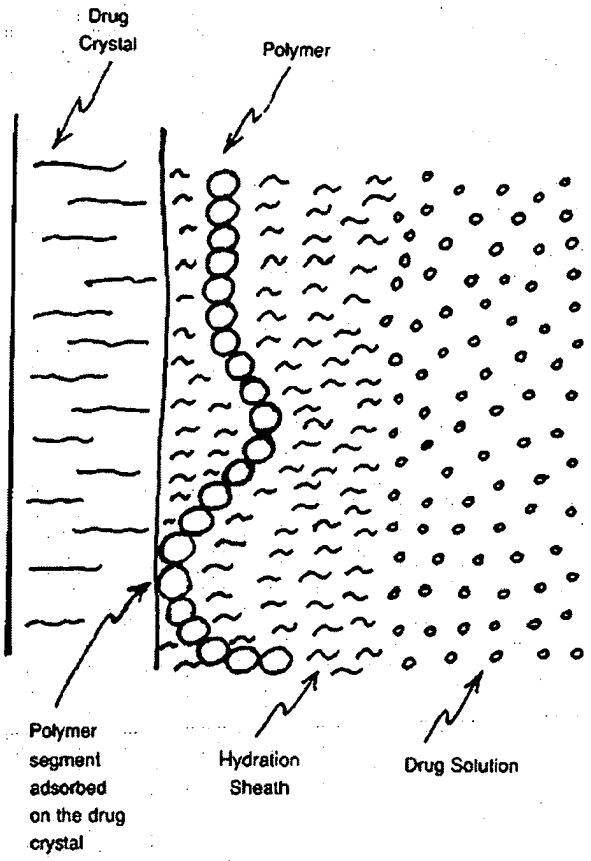

Fig. 18–7. Dissolution and crystallization of a drug in the presence of a polymer adsorbed on the drug crystal. (From K. H. Ziller and H. Rupprecht, Drug Dev. Ind. Pharm. 14, 2341, 1988, reproduced with permission of the copyright owner.)

cationic surfactant, has a positive charge and is strongly adsorbed at the particle surface. The positive end of the preservative molecule adsorbs on the negatively charged surface of the zinc oxide particles, forming a layer with the hydrocarbon chains oriented outward toward the dispersion medium. A second layer of preservative adsorbs at this monolayer, with the positively charged groups now directed toward the dispersion medium. Thus, the physical stability of the suspension may be enhanced owing to the repulsion of like-charged particles. However, the strong adsorption of the preservative on the zinc oxide particles reduces the biologically active free fraction of preservative in the dispersion medium, and the microbiologic activity is diminished.

EMULSIONS

An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules (the dispersed phase)

in the other liquid phase (the continuous phase), stabilized by the presence of an *emulsifying agent*. The various types of emulsifying agents are discussed later in this section. Either the dispersed phase or the continuous phase may range in consistency from that of a mobile liquid to a semisolid. Thus, emulsified systems range from lotions of relatively low viscosity to ointments and creams, which are semisolid in nature. The particle diameter of the dispersed phase generally extends from about 0.1 to 10 μm, although particle diameters as small as 0.01 μ and as large as 100 μm are not uncommon in some preparations.

Emulsion type. Invariably, one liquid phase in an emulsion is essentially polar (e.g., aqueous), while the other is relatively nonpolar (e.g., an oil). When the oil phase is dispersed as globules throughout an aqueous continuous phase, the system is referred to as an *oil-in-water* (*o/w*) emulsion. When the oil phase serves as the continuous phase, the emulsion is spoken of as a *water-in-oil* (*w/o*) product. Medicinal emulsions for oral administration are usually of the *o/w* type and require the use of an *o/w* emulsifying agent. These include synthetic nonionic surfactants, acacia, tragacanth, and gelatin. Not all emulsions that are consumed, however, belong to the *o/w* type. Certain foods such as butter and some salad dressings are *w/o* emulsions.

Externally applied emulsions may be *o/w* or *w/o*, the former employing the following emulsifiers in addition to the ones mentioned previously: sodium lauryl sulfate, triethanolamine stearate, monovalent soaps such as sodium oleate, and self-emulsifying glyceryl monostearate, that is, glyceryl monostearate mixed with a small amount of a monovalent soap or an alkyl sulfate. Pharmaceutical *w/o* emulsions are used almost exclusively for external application and may contain one or several of the following emulsifiers: polyvalent soaps such as calcium palmitate, sorbitan esters (*Spans*), cholesterol, and wool fat.

Several methods are commonly used to determine the type of an emulsion. A small quantity of a water-soluble dye such as methylene blue or brilliant blue FCF may be dusted on the surface of the emulsion. If water is the external phase (i.e., if the emulsion is of the *o/w* type), the dye will dissolve and uniformly diffuse throughout the water. If the emulsion is of the *w/o* type, the particles of dye will lie in clumps on the surface. A second method involves dilution of the emulsion with water. If the emulsion mixes freely with the water, it is of the *o/w* type. Another test uses a pair of electrodes connected to an external electric source and immersed in the emulsion. If the external phase is water, a current will pass through the emulsion and can be made to deflect a voltmeter needle or cause a light in the circuit to glow. If the oil is the continuous phase, the emulsion fails to carry the current.

Pharmaceutical Applications. An *o/w* emulsion is a convenient means of orally administering water-insoluble liquids, especially when the dispersed phase has an unpleasant taste. More significant in contemporary pharmacy is the observation that some oil-soluble compounds, such as some of the vitamins, are absorbed more completely when emulsified than when administered orally as an oily solution. The use of intravenous emulsions has been studied as a means of maintaining debilitated patients who are unable to assimilate materials administered orally. Tarr et al.[25] prepared emulsions of taxol, a compound with antimitotic properties, for intravenous administration as an alternative method to the use of cosolvents in taxol administration. Davis and Hansrani[26] studied the influence of droplet size and emulsifying agents on the phagocytosis of lipid emulsions. When the emulsion is administered intravenously, the droplets are normally rapidly taken up by the cells of the reticuloendothelial system, in particular the fixed macrophages in the liver. The rate of clearance by the macrophages increases as the droplet size becomes larger or the surface charge, either positive or negative, increases. Therefore, emulsion droplets stabilized by a nonionic surfactant (zero surface charge) were cleared much more slowly than the droplets stabilized by negatively charged phospholipids. Radiopaque emulsions have found application as diagnostic agents in x-ray examinations.

Emulsification is widely used in pharmaceutical and cosmetic products for external use. This is particularly so with dermatologic and cosmetic lotions and creams since a product that spreads easily and completely over the affected area is desired. Such products can now be formulated to be water washable and nonstaining and, as such, are obviously more acceptable to the patient and physician than some of the greasy products used a decade or more ago. Emulsification is used in aerosol products to produce foams. The propellant that forms the dispersed liquid phase within the container vaporizes when the emulsion is discharged from the container. This results in the rapid formation of a foam.

THEORIES OF EMULSIFICATION

There is no universal theory of emulsification, because emulsions can be prepared using several different types of emulsifying agent, each of which depends for its action on a different principle to achieve a stable product. For a theory to be meaningful, it should be capable of explaining (1) the stability of the product and (2) the type of emulsion formed. Let us consider what happens when two immiscible liquids are agitated together so that one of the liquids is dispersed as small droplets in the other. Except in the case of very dilute oil-in-water emulsions (oil hydrosols), which are somewhat stable, the liquids separate rapidly into two clearly defined layers. Failure of two immiscible liquids to remain mixed is explained by the fact that the *cohesive* force between the molecules of each separate liquid is greater than the *adhesive* force between the

two liquids. The cohesive force of the individual phases is manifested as an interfacial energy or tension at the boundary between the liquids, as explained in Chapter 14.

When one liquid is broken into small particles, the interfacial area of the globules constitutes a surface that is enormous compared with the surface area of the original liquid. If 1 cm^3 of mineral oil is dispersed into globules having a volume–surface diameter d_{vs} of 0.01 μm (10^{-6} cm) in 1 cm^3 of water so as to form a fine emulsion, the surface area of the oil droplets becomes 600 square meters. The surface free energy associated with this area is about 34×10^7 ergs, or 8 calories. The total volume of the system, however, has not increased; it remains at 2 cm^3. The calculations are made by use of equations (16–15) and (16–17), p. 436, from which

$$S_v = \frac{6}{d_{vs}}$$

$$S_v = \frac{6}{10^{-6}} = 6 \times 10^6 \text{ cm}^2 = 600 \text{ m}^2$$

The work input or surface free energy increase is given by the equation $W = \gamma_{ow} \times \Delta A$, and the interfacial tension γ_{ow} between mineral oil and water is 57 dyne/cm (erg/cm^2).

$$W = 57 \text{ erg/cm}^2 \times (6 \times 10^6 \text{ cm}^2)$$

$$= 34 \times 10^7 \text{ ergs} = 34 \text{ joules}$$

and since

$$1 \text{ cal} = 4.184 \text{ joules}$$

$$34/4.184 = 8 \text{ calories}$$

In summary, if 1 cm^3 of mineral oil is mixed with 1 cm^3 of water to produce fine particles (d_{vs} = 0.01 μm), the total surface is equivalent to an area slightly greater than that of a basketball court, or about 600 square meters! (In real emulsions, the particles are ordinarily about 10 to 100 times larger than this, and the surface area is proportionately smaller.) The increase in energy, 8 calories, associated with this enormous surface is sufficient to make the system thermodynamically unstable, hence the droplets have a tendency to coalesce.

To prevent coalescence or at least to reduce its rate to negligible proportions, it is necessary to introduce an emulsifying agent that will form a film around the dispersed globules. Emulsifying agents may be divided into three groups, as follows:

(1) Surface-active agents, which are adsorbed at oil–water interfaces to form monomolecular films and reduce interfacial tension. These agents have been discussed in detail in Chapter 14, dealing with interfacial phenomena.

(2) Hydrophilic colloids (discussed in Chapter 15), which form a *multi*molecular film around the dispersed droplets of oil in an *o/w* emulsion.[27,28]

(3) Finely divided solid particles, which are adsorbed at the interface between two immiscible liquid phases and form what amounts to a film of particles around the dispersed globules. The factor common to all three classes of emulsifying agent is the formation of a film, whether it be monomolecular, multimolecular, or particulate.

On this basis, we can now discuss some of the more important theories relating to the stability and type of emulsion formed.

Examples of typical emulsifying agents are given in Table 18–1.

Monomolecular Adsorption. Surface-active agents, or amphiphiles, reduce interfacial tension because of their adsorption at the oil–water interface to form monomolecular films. Since the surface free energy increase W equals $\gamma_{o/w} \times \Delta A$, and since we must, of necessity, retain a high surface area for the dispersed phase, any reduction in $\gamma_{o/w}$, the interfacial tension, will reduce the surface free energy and hence the tendency for coalescence. It is not unusual for a good emulsifying agent of this type to reduce the interfacial tension to 1 dyne/cm; we can therefore reduce the surface free energy of the system to approximately one sixtieth of that calculated earlier.

The reduction in surface free energy is of itself probably not the main factor involved. Of more likely

TABLE 18–1. ***Some Typical Emulsifying Agents***

Name	Class	Type of Emulsion Formed
Triethanolamine oleate	Surface-active agent (anionic)	*o/w* (HLB = 12)
N-cetyl *N*-ethyl morpholinum ethosulfate (Atlas G-263)	Surface-active agent (cationic)	*o/w* (HLB = 25)
Sorbitan mono-oleate (Atlas Span 80)	Surface-active-agent (nonionic)	*w/o* (HLB = 4.3)
Polyoxyethylene sorbitan mono-oleate (Atlas Tween 80)	Surface-active agent (nonionic)	*o/w* (HLB = 15)
Acacia (salts of *d*-glucuronic acid)	Hydrophilic colloid	*o/w*
Gelatin (polypeptides and aminoacids)	Hydrophilic colloid	*o/w*
Bentonite (hydrated aluminum silicate)	Solid particle	*o/w* (and *w/o*)
Veegum (magnesium aluminum silicate	Solid particle	*o/w*
Carbon black	Solid particle	*w/o*

significance is the fact that the dispersed droplets are surrounded by a coherent monolayer that helps to prevent coalescence between two droplets as they approach one another. Ideally, such a film should be flexible so that it is capable of reforming rapidly if broken or disturbed. An additional effect promoting stability is the presence of a surface charge (see p. 387), which will cause repulsion between adjacent particles.

In practice, combinations of emulsifiers rather than single agents are used most frequently today in the preparations of emulsions. In 1940, Schulman and Cockbain[29] first recognized the necessity of a predominantly hydrophilic emulsifier in the aqueous phase and a hydrophobic agent in the oil phase to form a complex film at the interface. Three mixtures of emulsifying agents at the oil–water interface are depicted in Figure 18–8. The combination of sodium cetyl sulfate and cholesterol leads to a complex film (Fig. 18–8*a*) that produces an excellent emulsion. Sodium cetyl sulfate and oleyl alcohol do not form a closely packed or condensed film (Fig. 18–8*b*), and consequently, their combination results in a poor emulsion. In Figure 18–8*c*, cetyl alcohol and sodium oleate produce a close-packed film, but complexation is negligible, and again a poor emulsion results.

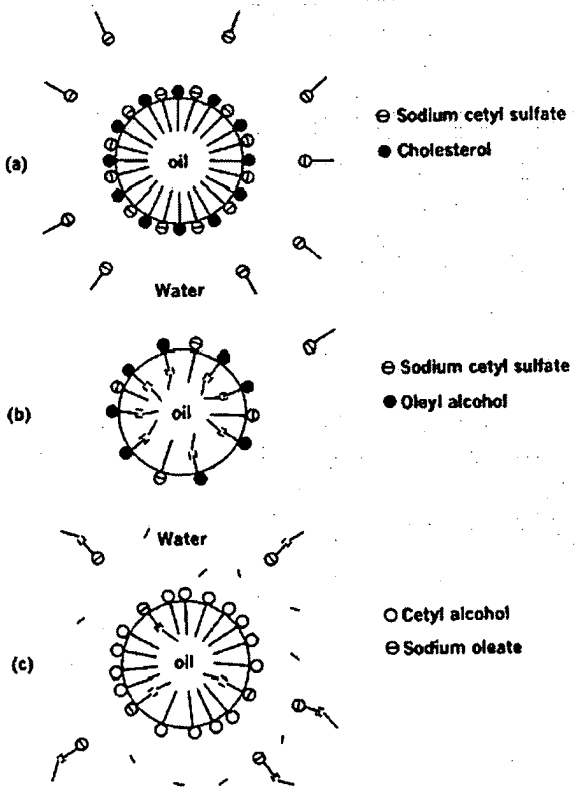

Fig. 18–8. Representations of combinations of emulsifying agents at the oil–water interface of an emulsion. (After J. H. Schulman and E. G. Cockbain, Trans. Faraday Soc. 36, 651, 1940.)

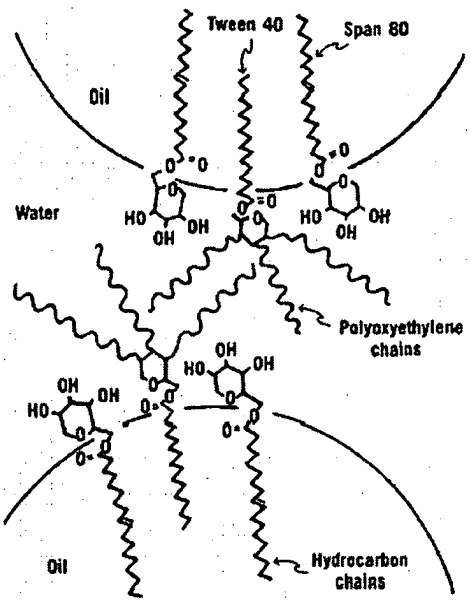

Fig. 18–9. Schematic of oil droplets in an oil–water emulsion, showing the orientation of a Tween and a Span molecule at the interface. (From J. Boyd, C. Parkinson and P. Sherman, J. Coll. Interface Sci. 41, 359, 1972, reproduced with permission of the copyright owner.)

Atlas-ICI* recommends that a hydrophilic Tween be combined with a lipophilic Span, varying the proportions so as to produce the desired *o/w* or *w/o* emulsion.[30] Boyd et al.[31] discussed the molecular association of Tween 40 and Span 80 in stabilizing emulsions. In Figure 18–9, the hydrocarbon portion of the Span 80 (sorbitan mono-oleate) molecule lies in the oil globule and the sorbitan radical lies in the aqueous phase. The bulky sorbitan heads of the Span molecules prevent the hydrocarbon tails from associating closely in the oil phase. When Tween 40 (polyoxyethylene sorbitan monopalmitate) is added, it orients at the interface such that part of its hydrocarbon tail is in the oil phase, and the remainder of the chain, together with the sorbitan ring and the polyoxyethylene chains, is located in the water phase. It is observed that the hydrocarbon chain of the Tween 40 molecule is situated in the oil globule between the Span 80 chains, and this orientation results in effective van der Waals attraction. In this manner, the interfacial film is strengthened and the stability of the *o/w* emulsion is increased against particle coalescence. The same principle of mixed emulsifying agents may be applied in the use of combinations such as

*Atlas surfactants, ICI United States, Inc., Wilmington, Del.

sodium stearate and cholesterol, sodium lauryl sulfate and glyceryl monostearate, and tragacanth and Span. Chun et al.[32] determined the hydrophile–lipophile balance of some natural agents and further discussed the principle of mixed emulsifiers.

The type of emulsion that is produced, *o/w* or *w/o*, depends primarily on the property of the emulsifying agent. This characteristic is referred to as the *hydrophile–lipophile* balance, that is, the polar–nonpolar nature of the emulsifier. In fact, whether a surfactant is an emulsifier, wetting agent, detergent, or solubilizing agent may be predicted from a knowledge of the hydrophile–lipophile balance, as discussed in a previous chapter (p. 371). In an emulsifying agent, such as sodium stearate, $C_{17}H_{35}COONa$, the nonpolar hydrocarbon chain, $C_{17}H_{35}$—, is the *lipophilic* or "oil-loving" group; the carboxyl group, —COONa, is the *hydrophilic* or "water-loving" portion. The balance of the hydrophilic and lipophilic properties of an emulsifier (or combination of emulsifiers) determines whether an *o/w* or *w/o* emulsion will result. In general, *o/w* emulsions are formed when the HLB of the emulsifier is within the range of about 9 to 12, and *w/o* emulsions are formed when the range is about 3 to 6. An emulsifier with a high HLB, such as a blend of Tween 20 and Span 20, will form an *o/w* emulsion. On the other hand, Span 60 alone, having an HLB of 4.7, tends to form a *w/o* emulsion.

It would appear, therefore, that the type of emulsion is a function of the relative solubility of the surfactant, the phase in which it is more soluble being the continuous phase. This is sometimes referred to as the *rule of Bancroft*, who observed this phenomenon in 1913. Thus, an emulsifying agent with a high HLB is preferentially soluble in water and results in the formation of an *o/w* emulsion. The reverse situation is true with surfactants of low HLB, which tend to form *w/o* emulsions. Beerbower, Nixon, and Hill[33] suggested an explanation for emulsion type and stability and devised a general scheme for emulsion formulation based on the Hildebrand and Hansen solubility parameters (pp. 224, 225).

Multimolecular Adsorption and Film Formation. Hydrated lyophilic colloids have been used for many years as emulsifying agents, although their use is declining because of the large number of synthetic surfactants now available. In a sense, they may be regarded as surface active since they appear at the oil–water interface. They differ, however, from the synthetic surface-active agents in that (1) they do not cause an appreciable lowering of interfacial tension, and (2) they form a multi- rather than a monomolecular film at the interface. Their action as emulsifying agents is due mainly to the latter effect, for the films thus formed are strong and resist coalescence. An auxiliary effect promoting stability is the significant increase in the viscosity of the dispersion medium. Since the emulsifying agents that form multilayer films around the droplets are invariably hydrophilic, they tend to promote the formation of *o/w* emulsions.

Solid Particle Adsorption. Finely divided solid particles that are wetted to some degree by both oil and water can act as emulsifying agents. This results from their being concentrated at the interface, where they produce a particulate film around the dispersed droplets so as to prevent coalescence. Powders that are wetted preferentially by water form *o/w* emulsions, whereas those more easily wetted by oil form *w/o* emulsions.

PHYSICAL STABILITY OF EMULSIONS

Probably the most important consideration with respect to pharmaceutical and cosmetic emulsions is the stability of the finished product. The stability of a pharmaceutical emulsion is characterized by the absence of coalescence of the internal phase, absence of creaming, and maintenance of elegance with respect to appearance, odor, color, and other physical properties. Some workers define instability of an emulsion only in terms of agglomeration of the internal phase and its separation from the product. Creaming, resulting from flocculation and concentration of the globules of the internal phase, sometimes is not considered as a mark of instability. An emulsion is a dynamic system, however, and flocculation and resultant creaming represent potential steps toward complete coalescence of the internal phase. Furthermore, in the case of pharmaceutical emulsions, creaming results in a lack of uniformity of drug distribution and, unless the preparation is thoroughly shaken before administration, leads to variable dosage. Certainly, the eye-appeal of an emulsion is affected by creaming, and this is just as real a problem to the pharmaceutical compounder as is separation of the internal phase.

Another phenomenon important in the preparation and stabilization of emulsions is *phase inversion*, which can be an aid or a detriment in emulsion technology. Phase inversion involves the change of emulsion type, from *o/w* to *w/o* or vice versa. Should phase inversion occur following preparation, it may logically be considered as an instance of instability.

In the light of these considerations, the instability of pharmaceutical emulsions may be classified as follows:

(*a*) flocculation and creaming
(*b*) coalescence and breaking
(*c*) miscellaneous physical and chemical changes
(*d*) phase inversion

Creaming and Stokes' Law. Those factors that find importance in the creaming of an emulsion are related by Stokes' law, equation (18–2) (p. 479). The limitations of this equation to actual systems have been discussed previously for suspensions (p. 479), and these apply equally to emulsified systems.

Analysis of the equation shows that if the dispersed phase is less dense than the continuous phase, which is

generally the case in *o/w* emulsions, the velocity of sedimentation becomes negative, that is, an upward *creaming* results. If the internal phase is heavier than the external phase, the globules settle, a phenomenon customarily noted in *w/o* emulsions in which the internal aqueous phase is more dense than the continuous oil phase. This effect may be referred to as *creaming in a downward direction*. The greater the difference between the density of the two phases, the larger the oil globules and the less viscous the external phase, the greater is the rate of creaming. By increasing the force of gravity through centrifugation, the rate of creaming may also be increased. The diameter of the globules is seen to be a major factor in determining the rate of creaming. Doubling the diameter of the oil globules increases the creaming rate by a factor of four.

Example 18–5. Consider an *o/w* emulsion containing mineral oil with a specific gravity of 0.90 dispersed in an aqueous phase having a specific gravity of 1.05. If the oil particles have an average diameter of 5 μm or 5×10^{-4} cm, the external phase has a viscosity of 0.5 poise (0.5 dyne sec/cm^2 or 0.5 g/cm sec), and the gravity constant is 981 cm/sec^2, what is the velocity of creaming in cm per day?

$$v = \frac{(5 \times 10^{-4})^2 \times (0.90 - 1.05) \times 981}{18 \times 0.5}$$

$$= -4.1 \times 10^{-6} \text{ cm/sec}$$

and since a 24-hour day contains 86,400 sec, the rate of upward creaming, $-v$, is

$$-v = 4.1 \times 10^{-6} \text{ cm/sec} \times 86{,}400 \text{ sec/day} = 0.35 \text{ cm/day}$$

The factors in Stokes' equation may be altered to reduce the rate of creaming in an emulsion. The viscosity of the external phase can be increased without exceeding the limits of acceptable consistency by adding a *viscosity improver* or *thickening agent* such as methylcellulose, tragacanth, or sodium alginate. The particle size of the globules may be reduced by homogenization; this, in fact, is the basis for the stability against creaming of homogenized milk. If the average particle size of the emulsion in the example just given is reduced to 1 μm or one fifth of the original value, the rate of creaming is reduced to 0.014 cm per day or about 5 cm per year. Actually, when the particles are reduced to a diameter below 2 to 5 μm, Brownian motion at room temperature exerts sufficient influence so that the particles settle or cream slower than predicted by Stokes' law.

Little consideration has been given to the adjustment of densities of the two phases in an effort to reduce the rate of creaming. Theoretically, adjusting the external and internal phase densities to the same value should eliminate the tendency to cream. This condition is seldom realized, however, since temperature changes alter the densities. Some research workers have increased the density of the oil phase by the addition of oil-soluble substances, such as α-bromonaphthalene, bromoform, and carbon tetrachloride, which, however, cannot be used in medicinal products. Mullins and Becker[34] added a food grade of a brominated oil to adjust the densities in pharmaceutical emulsions.

Equation (18–2) gives the rate of creaming of a single droplet of the emulsion, whereas one is frequently interested in the rate of creaming at the center of gravity of the mass of the disperse phase. Greenwald[35] has developed an equation for the mass creaming rate, to which the interested reader is referred for details.

Coalescence and Breaking. Creaming should be considered as separate from breaking, since creaming is a reversible process, whereas breaking is irreversible. The cream floccules may be redispersed easily, and a uniform mixture is reconstituted from a creamed emulsion by agitation, since the oil globules are still surrounded by a protective sheath of emulsifying agent. When breaking occurs, simple mixing fails to resuspend the globules in a stable emulsified form, since the film surrounding the particles has been destroyed and the oil tends to coalesce. Considerable work has been devoted to the study of breaking instability. The effects of certain factors on breaking are summarized in the following paragraphs.

King[36] showed that reduction of particle size does not necessarily lead to increased stability. Rather, he concluded that an optimum degree of dispersion for each particular system exists for maximum stability. As in the case of solid particles, if the dispersion is nonuniform, the small particles wedge between larger ones, permitting stronger cohesion so that the internal phase may coalesce easily. Accordingly, a moderately coarse dispersion of uniform-sized particles should have the best stability. Viscosity alone does not produce stable emulsions; however, viscous emulsions may be more stable than mobile ones by virtue of the retardation of flocculation and coalescence. Viscous or "tacky" emulsifiers seem to facilitate shearing of the globules as the emulsion is being prepared in the mortar, but this bears little or no relationship to stability. Knoechel and Wurster[37] have shown that viscosity plays only a minor role in the gross stability of *o/w* emulsions. Probably an *optimum* rather than a *high* viscosity is needed to promote stability.

The *phase–volume ratio* of an emulsion has a secondary influence on the stability of the product. This term refers to the relative volumes of water and oil in the emulsion. As shown in the section on powders (p. 443), uniform spherical particles in loose packing have a porosity of 48% of the total bulk volume. The volume occupied by the spheres must then be 52%.

If the spheres are arranged in closest packing, theoretically they cannot exceed 74% of the total volume regardless of their size. Although these values do not consider the distortions of size and shape and the possibility of small particles lying between larger spheres, they do have some significance with respect to real emulsions. Ostwald[38] and others have shown that if one attempts to incorporate more than about 74% of oil in an *o/w* emulsion, the oil globules often coalesce and the emulsion breaks. This value, known as the *critical point*, is defined as the concentration of the internal

phase above which the emulsifying agent cannot produce a stable emulsion of the desired type. In some stable emulsions, the value may be higher than 74% owing to the irregular shape and size of the globules. Generally speaking, however, a phase–volume ratio of 50:50 (which approximates loose packing) results in about the most stable emulsion. This fact was discovered empirically by pharmacists many years ago, and most medicinal emulsions are prepared with a volume ratio of 50 parts of oil to 50 parts of water.

Emulsions can be stabilized by electrostatic repulsion between the droplets, that is, by increasing their zeta potential. Magdassi and Siman-Tov[39] used lecithin to stabilize perfluocarbon emulsions, which appear to be a good blood substitute. Lecithin is a mixture of phospholipids having a negative charge at physiologic pH. The stabilizing effect is due to the adsorption of lecithin at the droplet surface, which creates a negative charge and consequently electrostatic repulsion. Lecithin produces very stable emulsions of triglyceride acids in water for intravenous administration. However, the stability of these emulsions may be poor because in clinical practice they are mixed with electrolytes, amino acids, and other compounds for total parenteral nutrition. The addition of positively charged species such as sodium and calcium ions or cationic amino acids—the charge on the latter depending on the pH—reduces the zeta potential and may cause flocculation. Johnson et al.[40] studied the effect of heparin and various electrolytes, frequently used clinically, on the stability of parenteral emulsions. Heparin, an anticoagulant, is a negatively charged polyelectrolyte that causes rapid flocculation in emulsions containing calcium and lecithin. The critical flocculation concentration occurs at a specific zeta potential. The value of this zeta potential can be determined by plotting the flocculation rate against the surface potential and extrapolating to zero flocculation rate.[41] Johnson et al.[40] explained the destabilizing effect of heparin as follows. Divalent electrolytes such as calcium bind strongly to the surface of droplets stabilized with lecithin to form 1:2 ion–lipid complexes. This causes a charge reversal on the droplets, leading to positively charged particles. The droplets are then flocculated by a bridging of the negatively charged heparin molecules across the positively charged particles, as depicted in Figure 18–10.

When the oil particles, which usually carry a negative charge, are surrounded in an *o/w* emulsion by a film of emulsifier, particularly a nonionic agent, the electrokinetic effects are probably less significant than they are in suspensions in maintaining the stability of the system. The effect of electrolytes in these systems has been studied by Schott and Royce.[42] Probably the most important factors in the stabilization of an emulsion are the physical properties of the emulsifier film at the interface. To be effective, an emulsifier film must be both tough and elastic and should form rapidly during emulsification. Serrallach et al.[43] have measured the strength of the film at the interface. They found that a good emulsifying agent or emulsifier combination brings about a preliminary lowering of the interfacial tension to produce small uniform globules and forms

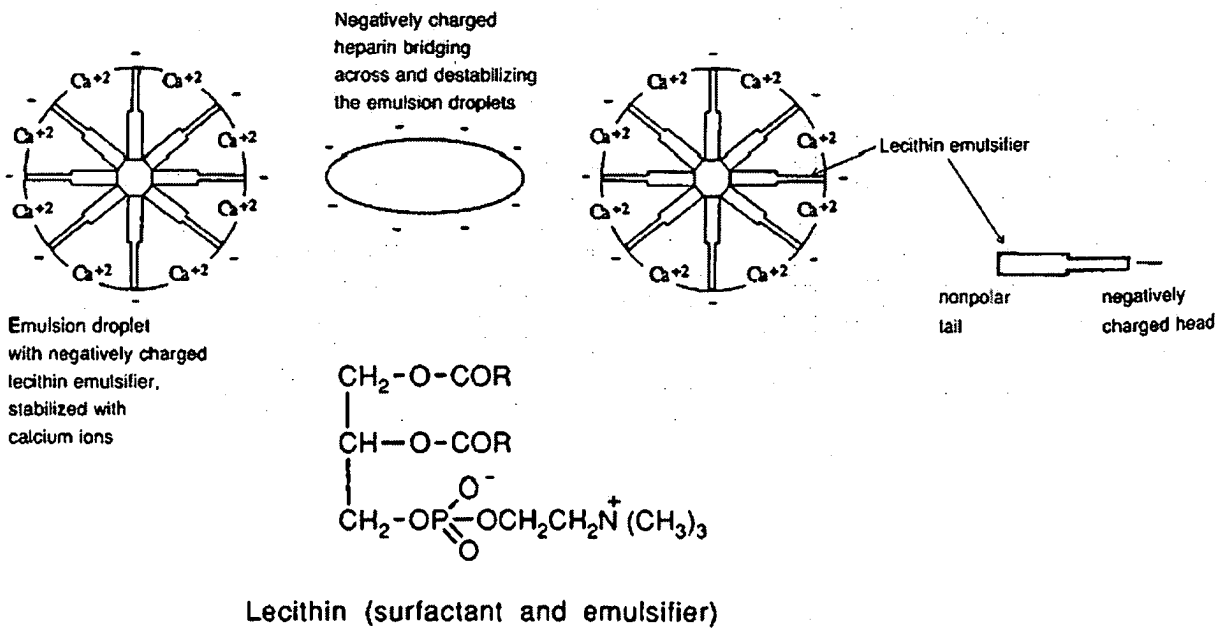

Fig. 18–10. Parenteral emulsion droplets in the presence of the negatively charged emulsifier lecithin, and stabilized by electrostatic repulsion by calcium ions. The emulsion may be flocculated and destabilized by the bridging effect of heparin, a negatively charged polyelectrolyte, which overcomes the stabilizing electrostatic repulsion of the Ca^{2+} ions. (From O. L. Johnson, C. Washington, S. S. Davis and K. Schaupp, Int. J. Pharm. 53, 237, 1989, reproduced with permission of the copyright owner.)

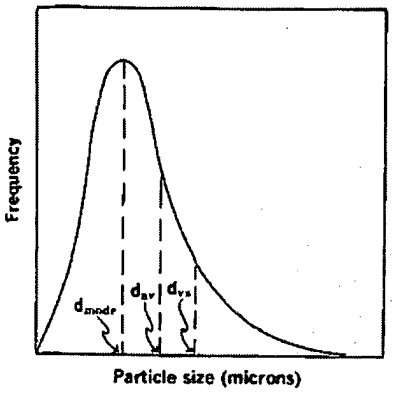

Fig. 18–11. Particle size distribution of an emulsion. Such curves ordinarily are skewed to the right as shown in the figure, and the mode diameter, i.e., the highest point on the curve or the most frequent value, is seen to occur at the lower end of the scale of diameters. The arithmetic mean diameter d_{av} will be found somewhat to the right of the mode in a right skewed distribution and the mean volume–surface diameter d_{vs} is to the right of the arithmetic mean.

rapidly to protect the globules from reaggregation during manufacture. The film then slowly increases in strength over a period of days or weeks.

Evaluation of Stability. According to King and Mukherjee,[44] the only precise method for determining stability involves a size-frequency analysis of the emulsion from time to time as the product ages. For rapidly breaking emulsions, macroscopic observation of separated internal phase is adequate, although the separation is difficult to read with any degree of accuracy. In the microscopic method, the particle diameters are measured, and a size-frequency distribution of particles ranging from 0.0 to 0.9 μm, 1.0 to 1.9 μm, 2.0 to 2.9 μm, etc., is made as shown in Figure 18–11. The particle size or diameter of the globules in micrometers is plotted on the horizontal axis against the frequency or number of globules in each size range on the vertical axis. Finkle et al.[45] were probably the first workers to use this method to determine the stability of emulsions. Since that time, many similar studies have been made. Schott and Royce[46] showed that the experimental problems involved in microscopic size determinations are Brownian motion, creaming, and field flow. Brownian motion affects the smallest droplets, causing them to move in and out of focus so that they are not consistently counted. Velocity of creaming is proportional to the square of the droplet diameter, and creaming focuses attention on the largest droplets because they move faster toward the cover glass than do smaller ones. *Field flow* is the motion of the entire volume of emulsion in the field due to the pressure exerted by the immersion objective on the cover glass, evaporation of the continuous phase, or convection currents resulting from heating by the light source. These workers[46] described an improved microscopic technique that overcomes these experimental problems and gives a more accurate measure of the droplet size.

An initial frequency distribution analysis on an emulsion is not an adequate test of stability, since stability is not related to initial particle size. Instead, one should perhaps consider the coalescence of the dispersed globules of an aging emulsion, or the separation of the internal phase from the emulsion over a period of time. Boyd et al.,[31] however, deemed this method unsatisfactory since the globules may undergo considerable coalescence before the separation becomes visible. These workers conducted particle size analyses with a Coulter centrifugal photosedimentometer. Mean volume diameters were obtained, and these were converted to number of globules per milliliter. King and Mukherjee[44] determined the specific interfacial area, that is, the area of interface per gram of emulsified oil, of each emulsion at successive times. They chose the reciprocal of the decrease of specific interfacial area with time as a measure of the stability of an emulsion.

Other methods used to determine the stability of emulsions are based on accelerating the separation process, which normally takes place under storage conditions. These methods employ freezing, thaw–freezing cycles, and centrifugation.

Merrill[47] introduced the centrifuge method to evaluate the stability of emulsions. Garrett, Vold, and others[48] have used the ultracentrifuge as an analytic technique in emulsion technology. Coulter counting (p. 434), turbidimetric analysis, and temperature tests have also been used in an effort to evaluate new emulsifying agents and to determine the stability of pharmaceutical emulsions. Garti and Magdassi[49] developed a method to evaluate the stability of oil–water viscous emulsions (ointments and cosmetic creams) containing nonionic surfactants. The method is based on electrical conductivity changes (see pp. 127–128 for conductivity) during nondestructive short heating–cooling–heating cycles. Conductivity curves are plotted during the temperature cycling. A stability index is defined as Δ/h, where h is the change in the conductivity between 35° and 45° C and Δ is the conductivity interval within the two heating curves at 35° C, as shown in Figure 18–12. The *stability index* indicates the relative change in conductivity between two cycles. The smaller the conductivity, the greater is the stability of the emulsion. The method was applied in a series of emulsions at different HLB's, emulsifier concentrations, and oil phase concentrations. The authors reviewed earlier work on electrical conductivity of emulsions as related to stability.

Phase Inversion. When controlled properly during the preparation of an emulsion, phase inversion often results in a finer product, but when it gets out of hand during manufacturing or is brought about by other factors after the emulsion is formed, it can cause considerable trouble.

An *o/w* emulsion stabilized with sodium stearate can be inverted to the *w/o* type by adding calcium chloride to form calcium stearate. inversion may also be produced by alterations in phase–volume ratio. In the manufacture of an emulsion, one can mix an *o/w*

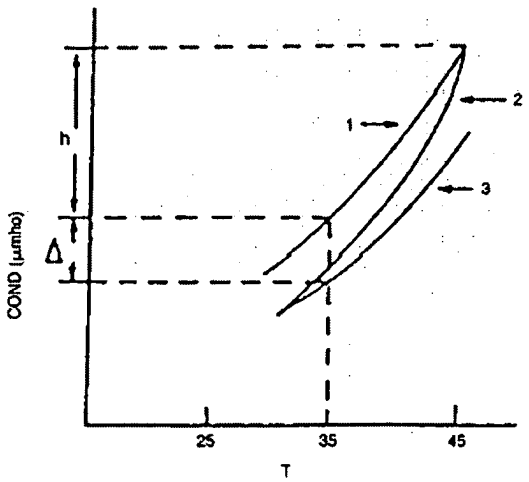

Fig. 18–12. A conductivity versus temperature plot involving successively (1) heating, (2) cooling, and (3) heating. (From N. Gartl and S. Magdassi, Drug Dev. Ind. Pharm. 8, 475, 1982, reproduced with permission of the copyright owner.)

emulsifier with an oil and then add a small amount of water. Since the volume of the water is small compared with the oil, the water is dispersed by agitation in the oil even though the emulsifier preferentially forms an oil-in-water system. As more water is slowly added, the inversion point is gradually reached and the water and emulsifier envelope the oil as small globules to form the desired *o/w* emulsion. This procedure is sometimes used in the preparation of commercial emulsions, and it is the principle of the *Continental method* used in compounding practice. The preparation of emulsions is discussed in books on general pharmacy and on compounding and dispensing.

PRESERVATION OF EMULSIONS

While it is not always necessary to achieve sterile conditions in an emulsion, even if the product is for topical or oral use, certain undesirable changes in the properties of the emulsion can be brought about by the growth of microorganisms. These include physical separation of the phases, discoloration, gas and odor formation, and changes in rheologic properties.[50] Emulsions for parenteral use obviously must be sterile.

The propagation of microorganisms in emulsified products is supported by one or more of the components present in the formulation. Thus, bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and vegetable gums present as thickeners, with a consequent deterioration of the emulsion. As a result, it is essential that emulsions are formulated to resist microbial attack by including an adequate concentration of preservative in the formulation. Given that the preservative has inherent activity against the type of contamination encountered, the main problem is obtaining an *adequate* concentration of preservative in the product. Some of the factors that must be considered to achieve this end are presented here.

Emulsions are heterogeneous systems in which partitioning of the preservative will occur between the oil and water phases. In the main, bacteria grow in the aqueous phase of emulsified systems, with the result that a preservative that is partitioned strongly in favor of the oil phase may be virtually useless at normal concentration levels because of the low concentration remaining in the aqueous phase. The phase–volume ratio of the emulsion is significant in this regard. In addition, the preservative must be in an un-ionized state to penetrate the bacterial membrane. Therefore, the activity of weak acid preservatives decreases as the pH of the aqueous phase rises. Finally, the preservative molecules must not be "bound" to other components of the emulsion since the complexes are ineffective as preservatives. Only the concentration of free, or unbound, preservative is effective. These points have been discussed in some detail in earlier sections of the text. The distribution of solutes between immiscible solvents was presented in Chapter 10, and the preservative action of weak acids in oil–water systems was introduced on page 240. Binding of molecules was discussed in Chapter 12, and the student should consult that chapter for information regarding the types of interaction that are possible between preservative molecules and the components of emulsions, such as nonionic surfactants. In addition to partitioning, ionization, and binding, the efficacy of a particular preservative is also influenced by emulsion type, nutritive value of the product, degree of aeration, and type of container used. These factors are discussed by Wedderburn.[50]

RHEOLOGIC PROPERTIES OF EMULSIONS

Emulsified products may undergo a wide variety of shear stresses during either preparation or use. In many of these processes, the flow properties of the product will be vital for the proper performance of the emulsion under the conditions of usage or preparation. Thus, spreadability of dermatologic and cosmetic products must be controlled to achieve a satisfactory preparation. The flow of a parenteral emulsion through a hypodermic needle, the removal of an emulsion from a bottle or tube, and the behavior of an emulsion in the various milling operations employed in the large-scale manufacture of these products all indicate the need for correct flow characteristics. Accordingly, it is important for the pharmacist to appreciate how formulation can influence the rheologic properties of emulsions.

The fundamentals of rheology have been discussed in Chapter 17. Most emulsions, except dilute ones, exhibit non-Newtonian flow, which complicates interpretation of data and quantitative comparisons between different systems and formulations. In a comprehensive review,

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CHAPTER 21

Coarse Dispersions

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This chapter will discuss the formation of suspensions and emulsions and the factors that influence their stability and performance as dosage forms. For the purpose of the present discussion, a dispersed system, or dispersion, will be regarded as a two-phase system in which one phase is distributed as particles or droplets in the second, or continuous, phase. In these systems, the dispersed phase frequently is referred to as the discontinuous or internal phase, and the continuous phase is called the external phase or dispersion medium. Discussion will be restricted to those solid-liquid and liquid-liquid dispersions that are of pharmaceutical significance, namely, suspensions and emulsions. However, more complicated phase systems (eg, a combination of liquid and liquid crystalline phases) can exist in emulsions. This situation will be discussed in the section dealing with emulsions.

All dispersions may be classified into three groups based of the size of the dispersed particles. Chapter 20 deals with one such group—colloidal dispersions—in which the size of the dispersed particles is in the range of approximately 10 Å to 0.5 μm. Molecular dispersions, the second group in this classification, are discussed in Chapter 19. The third group, consisting of *coarse dispersions* in which the particle size exceeds 0.5 μm, is the subject of this chapter. Knowledge of coarse dispersions is essential for the preparation of both pharmaceutical suspensions (solid-liquid dispersions) and emulsions (liquid-liquid dispersions).

The Dispersion Step

The pharmaceutical formulator is concerned primarily with producing a smooth, uniform, easily flowing (pouring or spreading) suspension or emulsion in which dispersion of particles can be effected with minimum expenditure of energy.

In preparing suspensions, particle-particle attractive forces need to be overcome by the high shearing action of such devices as the colloid mill, or by use of surface-active agents. The latter greatly facilitate wetting of lyophobic powders and assist in the removal of surface air that shearing alone may not remove; thus the clumping tendency of the particles is reduced. Moreover, lowering of the surface free energy by the adsorption of these agents directly reduces the thermodynamic driving force opposing dispersion of the particles.

In emulsification, shear rates are frequently necessary for dispersion of the internal phase into fine droplets. The shear forces are opposed by forces operating to resist distortion and subsequent breakup of the droplets. Again surface-active agents help greatly by lowering interfacial tension, which is the primary reversible component resisting droplet distortion. Surface-active agents also may play an important role in determining whether an oil-in-water (O/W) or a water-in-oil (W/O) emulsion preferentially survives the shearing action.

Once the process of dispersion begins there develops simultaneously a tendency for the system to revert to an energetically more stable state, manifested by flocculation, coalescence, sedimentation, crystal growth and caking phenomena. If these physical changes are not inhibited or controlled, successful dispersions will not be achieved or will be lost during shelf-life.

Interfacial Properties

Because suspensions and emulsions are dispersions of one phase within another, the process of dispersion creates a tremendous increase in interfacial area between the dispersed particles or droplets and the dispersion medium. When considering the interfacial properties of dispersed particles, two factors must be taken into account, regardless of whether the dispersed phase is solid or liquid. The first relates to an increase in the free energy of the surface as the particle size is reduced and the specific surface increased. The second deals with the presence of an electrical charge on the surface of the dispersed particles.

Surface Free Energy—When solid and liquid materials are reduced in size, they tend to agglomerate or stick together. This clumping, which can occur either in an air or liquid medium, is an attempt by the particles to reduce the excess free energy of the system. The increase in surface free energy is related to the increase in surface area produced when the mean particle size is reduced. It may be expressed as

$$\Delta F = \gamma \Delta A \qquad (1)$$

where ΔF is the increase in surface free energy in ergs, ΔA is the increase in surface area in cm^2 and γ is the interfacial tension in dynes/cm, between the dispersed particle or droplet and the dispersion medium. The smaller ΔF is, the more thermodynamically stable is the suspension of particles. A reduction in ΔF is effected often by the addition of a wetting agent (discussed in Chapter 19), which is adsorbed at the interface between the particle and the vehicle, thereby reducing the interfacial tension. This causes the particles to remain dispersed and settle relatively slowly. Unfortunately, in solid-liquid suspensions, the particles can form a hard cake at the bottom of the container when they eventually settle. Such a sediment can be extremely difficult to redisperse and lead to dosing errors when the product is administered to the patient.

Surface Potential—As discussed in Chapter 19, both attractive and repulsive forces exist between particles in a liquid medium. The balance between these opposing forces determines whether or not two particles approaching each other actually make contact or are repulsed at a certain distance of separation. While much of the theoretical work on electrical surface potentials has been carried out on lyophobic colloids, the theories developed in this area have been applied to suspensions and emulsions.[1]

Suspensions

A pharmaceutical suspension may be defined as a coar se dispersion containing finely divided insoluble material suspended in a liquid medium. Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, applied to the skin as topical preparations or used for ophthalmic purposes in the eye. They are an important class

of dosage form. Since some products occasionally are prepared in a dry form to be placed in suspension at the time of dispensing by the addition of an appropriate liquid vehicle, this definition is extended to include these products.

There are certain criteria that a well-formulated suspension should meet. The dispersed particles should be of such a size that they do not settle rapidly in the container. However, in the event that sedimentation does occur, the sediment must not form a hard cake. Rather, it should be capable of redispersion with a minimum of effort on the part of the patient. Finally, the product should be easy to pour, have a pleasant taste and be resistant to microbial attack.

The three major concerns associated with suspensions are (1) ensuring adequate dispersion of the particles in the vehicle, (2) minimizing settling of the dispersed particles and (3) preventing caking of these particles should a sediment form. Much of the following discussion will deal with the factors that influence these processes and the ways in which they can be minimized.

Flocculation and Deflocculation—Zeta potential, ψ_z, is a measurable indication of the potential existing at the surface of a particle. When ψ_z is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be *deflocculated*. Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of ψ_z. At some concentration of the added ion the electrical forces of repulsion are lowered sufficiently that the forces of attraction predominate. Under these conditions the particles may approach each other more closely and form loose aggregates, termed flocs. Such a system is said to be *flocculated*.

Some workers restrict the term *flocculation* to the aggregation brought about by chemical bridging; aggregation involving a reduction of repulsive potential at the double layer is referred to as *coagulation*. Other workers regard flocculation as aggregation in the secondary minimum of the potential energy curve of two interacting particles and coagulation as aggregation in the primary minimum. In the present chapter the term *flocculation* is used for all aggregation processes, irrespective of mechanism.

The continued addition of the flocculating agent can reverse the above process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anions onto positively charged, deflocculated particles in suspension will lead to flocculation. The addition of more anions eventually can generate a net negative charge on the particles. When this has achieved the required magnitude, deflocculation may occur again. The only difference from the starting system is that the net charge on the particles in their deflocculated state is negative rather than positive. Some of the major differences between suspensions of flocculated and deflocculated particles are presented in Table 1.

Flocculation Kinetics—The rate at which flocculation occurs is a consideration in the stability of suspended dispersions. Whether flocculation is judged to be rapid or slow depends on the presence of a repulsive barrier between adjacent particles. In the absence of such a barrier, and for a monodispersed system, rapid flocculation occurs at a rate given by the Smoluchowski equation

$$\delta N/\delta t = -4\pi DRN^2 \qquad (2)$$

where $\delta N/\delta t$ is the disappearance rate of particles/mL, R is the distance between the centers of the two particles in contact, N is the number of particles per mL and D is the diffusion coefficient. Under these conditions the rate is proportional to the square of the particle concentration. The presence or absence of an energy barrier is influenced strongly by the type and concentration of any electrolyte present. When an energy barrier does exist between adjacent particles, the flocculation rate likely will be much smaller than predicted by Eq 2.

Settling and its Control

In order to control the settling of dispersed material in suspension, the pharmacist must be aware of those physical factors that will affect the rate of sedimentation of particles under ideal and nonideal conditions. Also important are the various coefficients used to express the amount of flocculation in the system and the effect flocculation will have on the structure and volume of the sediment.

Sedimentation Rate

The rate at which particles in a suspension sediment is related to their size and density and the viscosity of the suspension medium. Brownian movement may exert a significant effect, as will the absence or presence of flocculation in the system.

Stokes' Law—The velocity of sedimentation of a uniform collection of spherical particles is governed by Stokes' law, expressed as

$$v = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta} \qquad (3)$$

where v is the terminal velocity in cm/sec, r is the radius of the particles in cm, ρ_1 and ρ_2 are the densities (g/cm^3) of the dispersed phase and the dispersion medium, respectively, g is the acceleration due to gravity (980.7 cm/sec^2) and η is the Newtonian viscosity of the dispersion medium in poises (g/cm sec). Stokes' law holds only if the downward motion of the particles is not sufficiently rapid to cause turbulence. Micelles and small phospholipid vesicles do not settle unless they are subjected to centrifugation.

While conditions in a pharmaceutical suspension are not in strict accord with those laid down for Stokes' law, Eq 3 provides those factors that can be expected to influence the rate of settling. Thus, sedimentation velocity will be reduced by

Table 1—Relative Properties of Flocculated and Deflocculated Particles in Suspension

Deflocculated	Flocculated
1. Particles exist in suspension as separate entities.	1. Particles form loose aggregates.
2. Rate of sedimentation is slow, since each particle settles separately and particle size is minimal.	2. Rate of sedimentation is high, since particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	3. A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed which is difficult, if not impossible, to redisperse.	4. The sediment is loosely packed and possesses a scaffold-like structure. Particles do not bond tightly to each other and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.
5. The suspension has a pleasing appearance, since the suspended material remains suspended for a relatively long time. The supernatant also remains cloudy, even when settling is apparent.	5. The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.

decreasing the particle size, provided the particles are kept in a deflocculated state. The rate of sedimentation will be an inverse function of the viscosity of the dispersion medium. However, too high a viscosity is undesirable, especially if the suspending medium is Newtonian rather than shear-thinning (see Chapter 22), since it then becomes difficult to redisperse material which has settled. It also may be inconvenient to remove a viscous suspension from its container. When the size of particles undergoing sedimentation is reduced to approximately 2 μm, random Brownian movement is observed and the rate of sedimentation departs markedly from the theoretical predictions of Stokes' law. The actual size at which Brownian movement becomes significant depends on the density of the particle as well as the viscosity of the dispersion medium.

Effect of Flocculation—In a deflocculated system containing a distribution of particle sizes, the larger particles naturally settle faster than the smaller particles. The very small particles remain suspended for a considerable length of time, with the result that no distinct boundary is formed between the supernatant and the sediment. Even when a sediment becomes discernible, the supernatant remains cloudy.

When the same system is flocculated (in a manner to be discussed later), two effects are immediately apparent. First, the flocs tend to fall together so that a distinct boundary between the sediment and the supernatant is readily observed; second, the supernatant is clear, showing that the very fine particles have been incorporated into the flocs. The initial rate of settling in flocculated systems is determined by the size of the flocs and the porosity of the aggregated mass. Under these circumstances it is perhaps better to use the term *subsidence*, rather than sedimentation.

Quantitative Expressions of Sedimentation and Flocculation

Frequently, the pharmacist needs to assess a formulation in terms of the amount of flocculation in the suspension and compare this with that found in other formulations. The two parameters commonly used for this purpose are outlined below.

Sedimentation Volume—The *sedimentation volume*, F, is the ratio of the equilibrium volume of the sediment, V_u, to the total volume of the suspension, V_0. Thus

$$F = V_u/V_0 \qquad (4)$$

As the volume of suspension which appears occupied by the sediment increases, the value of F, which normally ranges from nearly 0 to 1, increases. In the system where $F = 0.75$, for example, 75% of the total volume in the container is apparently occupied by the loose, porous flocs forming the sediment. This is illustrated in Fig. 1. When $F = 1$, no sediment is apparent even though the system is flocculated. This is the ideal suspension for, under these conditions, no sedimentation will occur. Caking also will be absent. Furthermore, the suspension is esthetically pleasing, there being no visible, clear supernatant.

Degree of Flocculation—A better parameter for comparing flocculated systems is the *degree of flocculation*, β, which relates the sedimentation volume of the flocculated suspension, F, to the sedimentation volume of the suspension when deflocculated, F_∞. It is expressed as

$$\beta = F/F_\infty \qquad (5)$$

The degree of flocculation is, therefore, an expression of the increased sediment volume resulting from flocculation. If, for example, β has a value of 5.0 (Fig 1), this means that the volume of sediment in the flocculated system is five times that in the deflocculated state. If a second flocculated formulation results in a value for β of say 6.5, this latter suspension obviously is preferred, if the aim is to produce as flocculated a product as possible. As the degree of flocculation in the system decreases, β approaches unity, the theoretical minimum value.

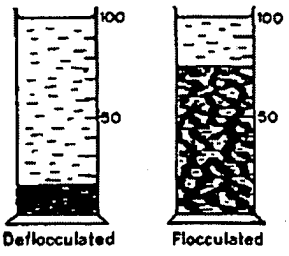


Fig 1. Sedimentation parameters of suspensions. Deflocculated suspension: $F_u = 0.15$. Flocculated suspension: $F = 0.75$; $\beta = 5.0$.

Formulation of Suspensions

The formulation of a suspension possessing optimal physical stability depends on whether the particles in suspension are to be flocculated or to remain deflocculated. One approach involves use of a structured vehicle to keep deflocculated particles in suspension; a second depends on controlled flocculation as a means of preventing cake formation. A third, a combination of the two previous methods, results in a product with optimum stability. The various schemes are illustrated in Fig 2.

Dispersion of Particles—The dispersion step has been discussed earlier in this chapter. Surface-active agents commonly are used as wetting agents; maximum efficiency is obtained when the HLB value lies within the range of 7 to 9. A concentrated solution of the wetting agent in the vehicle may be used to prepare a slurry of the powder; this is diluted with the required amount of vehicle. Alcohol and glycerin may be used sometimes in the initial stages to disperse the particles, thereby allowing the vehicle to penetrate the powder mass.

Only the minimum amount of wetting agent should be used, compatible with producing an adequate dispersion of the particles. Excessive amounts may lead to foaming or impart an undesirable taste or odor to the product. Invariably, as a result of wetting, the dispersed particles in the vehicle are deflocculated.

Structured Vehicles—Structured vehicles are generally aqueous solutions of polymeric materials, such as the hydrocolloids, which are usually negatively charged in aqueous

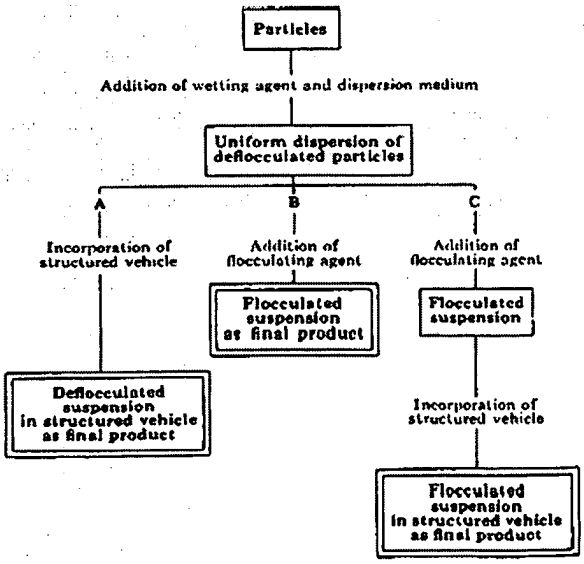


Fig 2. Alternative approaches to the formulation of suspensions.

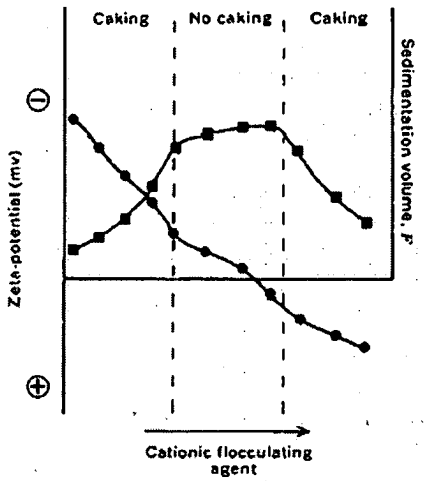


Fig 3. Typical relationship between caking, zeta potential and sedimentation volume, as a positively charged flocculating agent is added to a suspension of negatively charged particles. ●: zeta potential; ■: sedimentation volume.

solution. Typical examples are methycellulose, carboxymethylcellulose, bentonite and Carbopol. The concentration employed will depend on the consistency desired for the suspension which, in turn, will relate to the size and density of the suspended particles. They function as viscosity-imparting suspending agents and, as such, reduce the rate of sedimentation of dispersed particles.

The rheological properties of suspending agents are considered elsewhere (Chapter 22). Ideally, these form pseudoplastic or plastic systems which undergo shear-thinning. Some degree of thixotropy is also desirable. Non-Newtonian materials of this type are preferred over Newtonian systems because, if the particles eventually settle to the bottom of the container, their redispersion is facilitated by the vehicle thinning when shaken. When the shaking is discontinued, the vehicle regains its original consistency and the redispersed particles are held suspended. This process of redispersion, facilitated by a shear-thinning vehicle, presupposes that the deflocculated particles have not yet formed a cake. If sedimentation and packing have proceeded to the point where considerable caking has occurred, redispersion is virtually impossible.

Controlled Flocculation—When using this approach (see Fig 2 B and C), the formulator takes the deflocculated, wetted dispersion of particles and attempts to bring about flocculation by the addition of a flocculating agent; most commonly, these are electrolytes, polymers or surfactants. The aim is to *control* flocculation by adding that amount of flocculating agent which results in the maximum sedimentation volume.

Electrolytes are probably the most widely used flocculating agents. They act by reducing the electrical forces of repulsion between particles, thereby allowing the particles to form the loose flocs so characteristic of a flocculated suspension. Since the ability of particles to come together and form a floc depends on their surface charge, zeta potential measurements on the suspension, as an electrolyte is added, provide valuable information as to the extent of floculation in the system.

This principle is illustrated by reference to the following example, taken from the work of Haines and Martin.[2] Particles of sulfamerazine in water bear a negative charge. The serial addition of a suitable electrolyte, such as aluminum chloride, causes a progressive reduction in the zeta potential of the particles. This is due to the preferential adsorption of the trivalent aluminium cation. Eventually, the zeta potential will reach zero and then become positive as the addition of $AlCl_3$ is continued.

If sedimentation studies are run simultaneously on suspensions containing the same range of $AlCl_3$ concentrations, a relationship is observed (Fig. 3) between the sedimentation volume F, the presence or absence of caking and the zeta potential of the particles. In order to obtain a flocculated, noncaking suspension with the maximum sedimentation volume, the zeta potential must be controlled so as to lie within a certain range (generally less than 25 mV). This is achieved by the judicious use of an electrolyte.

A comparable situation is observed when a negative ion such as PO_4^{3-} is added to a suspension of positively charged particles such as bismuth subnitrate. Ionic and nonionic surfactants and lyophilic polymers also have been used to flocculate particles in suspension. Polymers, which act by forming a "bridge" between particles, may be the most efficient additives for inducing flocculation. Thus, it has been shown that the sedimentation volume is higher in suspensions flocculated with an anionic heteropolysaccharide than when electrolytes were used.

Work by Matthews and Rhodes,[3-5] involving both experimental and theoretical studies, has confirmed the formulation principles proposed by Martin and Haines. The suspensions used by Matthews and Rhodes contained 2.5% w/v of griseofulvin as a fine powder together with the anionic surfactant sodium dioxyethylated dodecyl sulfate (10^{-3} molar) as a wetting agent. Increasing concentrations of aluminum chloride were added and the sedimentation height (equivalent to the sedimentation volume, see page 280) and the zeta potential recorded. Flocculation occurred when a concentration of 10^{-3} molar aluminum chloride was reached. At this point the zeta potential had fallen from −46.4 mV to −17.0 mV. Further reduction of the zeta potential, to −4.5 mV by use of 10^{-2} molar aluminum chloride did not increase sedimentation height, in agreement with the principles shown in Fig. 3.

Matthews and Rhodes then went on to show, by computer analysis, that the DLVO theory (see page 264) predicted the results obtained, namely, that the griseofulvin suspensions under investigation would remain deflocculated when the concentration of aluminum chloride was 10^{-4} molar or less. Only at concentrations in the range of 10^{-3} to 10^{-2} molar aluminum chloride did the theoretical plots show deep primary minima, indicative of flocculation. These occurred at a distance of separation between particles of approximately 50Å, and led Matthews and Rhodes to conclude that coagulation had taken place in the primary minimum.

Schneider *et al*[6] have published details of a laboratory investigation (suitable for undergraduates) that combines calculations based on the DLVO theory carried out with an interactive computer program with actual sedimentation experiments performed on simple systems.

Flocculation in Structured Vehicles—The ideal formulation for a suspension would seem to be when flocculated particles are supported in a structured vehicle.

As shown in Fig 2 (under C), the process involves dispersion of the particles and their subsequent flocculation. Finally, a lyophilic polymer is added to form the structured vehicle. In developing the formulation, care must be taken to ensure the absence of any incompatibility between the flocculating agent and the polymer used for the structured vehicle. A limitation is that virtually all the structured vehicles in common use are hydrophilic colloids and carry a negative charge. This means that an incompatibility arises if the charge on the particles is originally negative. Flocculation in this instances requires the addition of a positively charged flocculating agent or ion; in the presence of such a material, the negatively charged suspending agent may coagulate and lose its suspendability. This situation does not arise with particles that bear a positive charge, as the negative flocculating agent which the formulator must employ is compatible with the similarly charged suspending agent.

Chemical Stability of Suspensions—Particles that are completely insoluble in a liquid vehicle are unlikely to undergo most chemical reactions leading to degradation. However, most drugs in suspension have a finite solubility, even though this may be of the order of fractions of a microgram per mL. As a result, the material in solution may be

susceptible to degradation. However, Tingstad *et al*[7] developed a simplified method for determining the stability of drugs in suspension. The approach is based on the assumptions that (1) degradation takes place only in the solution and is first order, (2) the effect of temperature on drug solubility and reaction rate conforms with classical theory, and (3) dissolution is not rate-limiting on degradation.

Preparation of Suspensions—The small-scale preparation of suspensions may be undertaken readily by the practicing pharmacist with the minimum of equipment. The initial dispersion of the particles is best carried out by trituration in a mortar, the wetting agent being added in small increments to the powder. Once the particles have been wetted adequately, the slurry may be transferred to the final container. The next step depends on whether the deflocculated particles are to be suspended in a structured vehicle, flocculated or flocculated and then suspended. Regardless of which of the alternative procedures outlined in Fig 2 is employed, the various manipulations can be carried out easily in the bottle, especially if an aqueous solution of the suspending agent has been prepared beforehand.

For detailed discussion of the methods used in the large-scale production of suspensions, see the relevant section in Chapter 86.

Emulsions

An emulsion is a dispersed system containing at least two immiscible liquid phases. The majority of conventional emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1 to 100 μm. As with suspensions, emulsions are thermodynamically unstable as a result of the excess free energy associated with the surface of the droplets. The dispersed droplets, therefore, strive to come together and reduce the surface area. In addition to this flocculation effect, also observed with suspensions, the dispersed particles can coalesce, or fuse, and this can result in the eventual destruction of the emulsion. In order to minimize this effect a third component, the *emulsifying agent*, is added to the system to improve its stability. The choice of emulsifying agent is critical to the preparation of an emulsion possessing optimum stability. The efficiency of present-day emulsifiers permits the preparation of emulsions which are stable for many months and even years, even though they are thermodynamically unstable.

In recent years, it has been recognized that complex multiple-phase combinations can exist in emulsions. Thus, liquid crystalline phases and gel structures can form from the combination of the basic three-component mixture of water, oil and surfactant (emulsifying agent). Often, these structures confer significant stability to the emulsion and therefore are to be desired. Such multiple-phase emulsions and their stability have been reviewed by Eccleston.[8]

Emulsions are widely used in pharmacy and medicine, and emulsified materials can possess advantages not observed when formulated in other dosage forms. Thus, certain medicinal agents having an objectionable taste have been made more palatable for oral administration when formulated in an emulsion. The principles of emulsification have been applied extensively in the formulation of dermatological creams and lotions. Intravenous emulsions of contrast media have been developed to assist the physician in undertaking X-ray examinations of the body organs while exposing the patient to the minimum of radiation. Considerable attention has been directed towards the use of sterile, stable intravenous emulsions containing fat, carbohydrate and vitamins all in one preparation. Such products are administered to patients unable to assimilate these vital materials by the normal oral route.

Emulsions offer potential in the design of systems capable of giving controlled rates of drug release and affording protection to drugs susceptible to oxidation or hydrolysis. There is still a need for well-characterized dermatological products with reproducible properties, regardless of whether these products are antibacterial, sustained-release, protective or emollient lotions, creams or ointments. The principle of emulsification is involved in an increasing number of aerosol products.

The pharmacist must be familiar with the types of emulsions and the properties and theories underlying their preparation and stability; such is the purpose of the remainder of this chapter. Microemulsions, which can be regarded as isotropic, swollen micellar systems are discussed in Chapter 86.

Emulsion Type and Means of Detection

A stable emulsion must contain at least three components; namely, the dispersed phase, the dispersion medium and the emulsifying agent. Invariably, one of the two immiscible liquids is aqueous while the second is an oil. Whether the aqueous or the oil phase becomes the dispersed phase depends primarily on the emulsifying agent used and the relative amounts of the two liquid phases. Hence, an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is termed an oil-in-water, O/W, emulsion. When water is the dispersed phase and an oil the dispersion medium, the emulsion is of the water-in-oil, W/O, type. Most pharmaceutical emulsions designed for oral administration are of the O/W type; emulsified lotions and creams are either O/W or W/O, depending on their use. Butter and salad creams are W/O emulsions.

So-called *multiple* emulsions have been developed with a view to delaying the release of an active ingredient. In these types of emulsions three phases are present, ie, the emulsion has the form W/O/W or O/W/O. In these "emulsions within emulsions," any drug present in the innermost phase must now cross two phase boundaries to reach the external, continuous, phase.

It is important for the pharmacist to know the type of emulsion he has prepared or is dealing with, since this can affect its properties and performance. Unfortunately, the several methods available can give incorrect results, and so the type of emulsion determined by one method should always be confirmed by means of a second method.

Dilution Test—This method depends on the fact that an O/W emulsion can be diluted with water and a W/O emulsion with oil. When oil is added to an O/W emulsion or water to a W/O emulsion, the additive is not incorporated into the emulsion and separation is apparent. The test is greatly improved if the addition of the water or oil is observed microscopically.

Conductivity Test—An emulsion in which the continuous phase is aqueous can be expected to possess a much higher conductivity than an emulsion in which the continuous phase is an oil. Accordingly, it frequently happens that when a pair of electrodes, connected to a lamp and an electrical source, are dipped into an O/W emulsion, the lamp lights due to passage of a current between the two electrodes. If the lamp does not light, it is assumed that the system is W/O.

Dye-Solubility Test—The knowledge that a water-soluble dye will dissolve in the aqueous phase of an emulsion while an oil-soluble dye will be taken up by the oil phase provides a third means of determining emulsion type. Thus, if microscopic examination shows that a water-soluble dye has been taken up by the continuous phase, we are dealing with an O/W emulsion. If the dye has not stained the continuous phase, the test is repeated using a small amount of an oil-soluble dye. Coloring of the continuous phase confirms that the emulsion is of the W/O type.

Formation and Breakdown of Dispersed Liquid Droplets

An emulsion exists as the result of two competing processes, namely, the dispersion of one liquid throughout another as droplets, and the combination of these droplets to reform the initial bulk liquids. The first process increases the free energy of the system, while the second works to reduce the free energy. Accordingly, the second process is spontaneous and continues until breakdown is complete; ie, the bulk phases are reformed.

It is of little use to form a well-dispersed emulsion if it quickly breaks down. Similarly, unless adequate attention is given to achieving an optimum dispersion during preparation, the stability of an emulsion system may be compromised from the start. Dispersion is brought about by well-designed and well-operated machinery, capable of producing droplets in a relatively short period of time. Such equipment is discussed in Chapter 86. The reversal back to the bulk phases is minimized by utilizing those parameters which influence the stability of the emulsion once it is formed.

Dispersion Process To Form Droplets—Consider two immiscible liquid phases in a test tube. In order to disperse one liquid as droplets within the other, the interface between the two liquids must be disturbed and expanded to a sufficient degree so that "fingers" or threads of one liquid pass into the second liquid, and *vice versa*. These threads are unstable, and become varicosed or beaded. The beads separate and become spherical, as illustrated in Fig 4. Depending on the agitation or the shear rate used, larger droplets are also deformed to give small threads, which in turn produce smaller drops.

The time of agitation is important. Thus, the mean size of droplets decreases rapidly in the first few seconds of agitation. The limiting size range is generally reached within 1 to 5 minutes, and results from the number of droplets coalescing being equivalent to the number of new droplets being formed. It is uneconomical to continue agitation any further.

The liquids may be agitated or sheared by several means. Shaking is employed commonly, especially when the components are of low viscosity. Intermittent shaking is frequently more efficient than continual shaking, possibly because the short time interval between shakes allows the thread which is forced across the interface time to break down into drops which are then isolated in the opposite phase. Continuous, rapid agitation tends to hinder this breakdown to form drops. A mortar and pestle is employed frequently in the extemporaneous preparation of emulsions. It is not a very efficient technique and is not used on a large scale. Improved dispersions are achieved by the use of high-speed mixers, blenders, colloid mills or homogenizers. Ultrasonic techniques also have been employed and are described in Chapter 86.

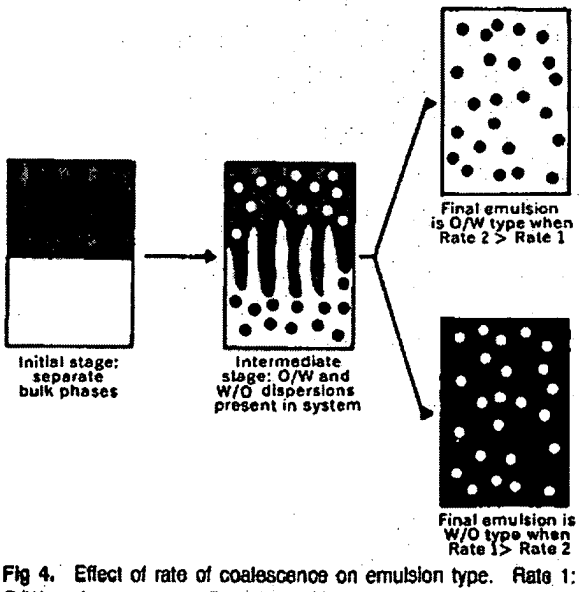


Fig 4. Effect of rate of coalescence on emulsion type. Rate 1: O/W coalescence rate; Rate 2: W/O coalescence rate. ●: oil; O: water. For an explanation of Rates 1 and 2, refer to the discussion of Davies on page 287.

The phenomenon of spontaneous emulsification, as the name implies, occurs without any external agitation. There is, however, an internal agitation arising from certain physicochemical processes that affect the interface between the two bulk liquids. For a description of this process, see Davies and Rideal in the *Bibliography*.

Coalescence of Droplets—Coalescence is a process distinct from flocculation (aggregation), which commonly precedes it. While flocculation is the clumping together of particles, coalescence is the fusing of the agglomerates into a larger drop, or drops. Coalescence usually is rapid when two immiscible liquids are shaken together, since there is no large energy barrier to prevent fusion of drops and reformation of the original bulk phases. When an emulsifying agent is added to the system, flocculation still may occur but coalescence is reduced to an extent depending on the efficacy of the emulsifying agent to form a stable, coherent interfacial film. It is therefore possible to prepare emulsions that are flocculated, yet which do not coalesce. In addition to the interfacial film around the droplets acting as a mechanical barrier, the drops also are prevented from coalescing by the presence of a thin layer of continuous phase between particles clumped together.

Davies[9] showed the importance of coalescence rates in determining emulsion type; this work is discussed in more detail on page 287.

Emulsifying Agent

The process of coalescence can be reduced to insignificant levels by the addition of a third component—the emulsifying agent or emulsifier. The choice of emulsifying agent is frequently critical in developing a successful emulsion, and the pharmacist should be aware of

The desirable properties of emulsifying agents.
How different emulsifiers act to optimize emulsion stability.
How the type and physical properties of the emulsion can be affected by the emulsifying agent.

Desirable Properties

Some of the desirable properties of an emulsifying agent are that it should

1. Be surface-active and reduce surface tension to below 10 dynes/cm.
2. Be adsorbed quickly around the dispersed drops as a condensed, nonadherent film which will prevent coalescence.
3. Impart to the droplets an adequate electrical potential so that mutual repulsion occurs.
4. Increase the viscosity of the emulsion.
5. Be effective in a reasonably low concentration.

Not all emulsifying agents possess these properties to the same degree; in fact, not every good emulsifier necessarily possesses all these properties. Further, there is no one "ideal" emulsifying agent because the desirable properties of an emulsifier depend, in part, on the properties of the two immiscible phases in the particular system under consideration.

Interfacial Tension—Lowering of interfacial tension is one way in which the increased surface free energy associated with the formation of droplets, and hence surface area, in an emulsion can be reduced (Eq 1). Assuming the droplets to be spherical, it can be shown that

$$\Delta F = \frac{6\gamma V}{d} \qquad (6)$$

where V is the volume of dispersed phase in mL and d is the mean diameter of the particles. In order to disperse 100 mL of oil as 1-μm (10^{-4}-cm) droplets in water when $\gamma_{o/w} = 50$ dynes/cm, requires an energy input of

$$\Delta F = \frac{6 \times 50 \times 100}{1 \times 10^{-4}} = 30 \times 10^7 \text{ ergs}$$

$$= 30 \text{ joules or } 30/4.184 = 7.2 \text{ cal}$$

In the above example the addition of an emulsifier that will reduce γ from 50 to 5 dynes/cm will reduce the surface free energy from 7.2 to around 0.7 cal. Likewise, if the interfacial tension is reduced to 0.5 dynes/cm, a common occurrence, the original surface free energy is reduced a hundredfold. Such a reduction can help to maintain the surface area generated during the dispersion process.

Film Formation—The major requirement of a potential emulsifying agent is that it readily form a film around each droplet of dispersed material. The main purpose of this film—which can be a monolayer, a multilayer or a collection of small particles adsorbed at the interface—is to form a barrier which prevents the coalescence of droplets that come into contact with one another. For the film to be an efficient barrier, it should possess some degree of surface elasticity and should not thin out and rupture when sandwiched between two droplets. If broken, the film should have the capacity to reform rapidly.

Electrical Potential—The origin of an electrical potential at the surface of a droplet has been discussed earlier in the chapter. Insofar as emulsions are concerned, the presence of a well-developed charge on the droplet surface is significant in promoting stability by causing repulsion between approaching drops. This potential is likely to be greater when an ionized emulsifying agent is employed.

Concentration of Emulsifier—The main objective of an emulsifying agent is to form a condensed film around the droplets of the dispersed phase. An inadequate concentration will do little to prevent coalescence. Increasing the emulsifier concentration above an optimum level achieves little in terms of increased stability. In practice the aim is to use the minimum amount consistent with producing a satisfactory emulsion.

It frequently helps to have some idea of the amount of emulsifier required to form a condensed film, one molecule thick, around each droplet. Suppose we wish to emulsify 50 g of an oil, density = 1.0, in 50 g of water. The desired particle diameter is 1 μm. Thus

Particle diameter = 1 μm = 1×10^{-4} cm
Volume of particle = $(\pi d^3/6) = 0.524 \times 10^{-12}$ cm^3
Total number of particles in 50 g = $(50/0.524 \times 10^{-12}) = 95.5 \times 10^{12}$
Surface area of each particle = $\pi d^2 = 3.142 \times 10^{-8}$ cm^2
Total surface area = $3.142 \times 10^{-8} \times 95.5 \times 10^{12} = 300 \times 10^4$ cm^2

If the area each molecule occupies at the oil/water interface is 30 Å^2 (30×10^{-16} cm^2), we require

$$\frac{300 \times 10^4}{30 \times 10^{16}} = 1 \times 10^{21} \text{ molecules}$$

A typical emulsifying agent might have a molecular weight of 1000. Thus, the required weight is

$$\frac{1000 \times 10^{21}}{6.023 \times 10^{23}} = 1.66 \text{ g}$$

To emulsify 10 g of oil would require 0.33 g of the emulsifying agent, etc. While the approach is an oversimplification of the problem, it does at least allow the formulator to make a reasonable estimate of the required concentration of emulsifier.

Emulsion Rheology—The emulsifying agent and other components of an emulsion can affect the rheologic behavior of an emulsion in several ways and these are summarized in Table 2.[10] It should be borne in mind that the droplets of the internal phase are deformable under shear and that the adsorbed layer of emulsifier affects the interactions between adjacent droplets and also between a droplet and the continuous phase.

Table 2—Factors Influencing Emulsion Viscosity[10]

1. Internal phase
   a. Volume concentration (ϕ); hydrodynamic interaction between globules; flocculation, leading to formation of globule aggregates.
   b. Viscosity (η_i); deformation of globules in shear.
   c. Globule size, and size distribution, technique used to prepare emulsion; interfacial tension between the two liquid phases: globule behavior in shear; interaction with continuous phase; globule interaction.
   d. Chemical constitution.
2. Continuous phase
   a. Viscosity (η_0), and other rheological properties.
   b. Chemical constitution, polarity, pH; potential energy of interaction between globules.
   c. Electrolyte concentration if polar medium.
3. Emulsifying agent
   a. Chemical constitution; potential energy of interaction between globules.
   b. Concentration, and solubility in internal and continuous phases; emulsion type; emulsion inversion; solubilization of liquid phases in micelles.
   c. Thickness of film adsorbed around globules, and its rheological properties, deformation of globules in shear; fluid circulation within globules.
   d. Electroviscous effect.
4. Additional stabilizing agents
   Pigments, hydrocolloids, hydrous oxides; effect on rheologic properties of liquid phases, and interfacial boundary region.

The means by which the rheological behavior of emulsions can be controlled have been discussed by Rogers.[11]

Mechanism of Action

Emulsifying agents may be classified in accordance with the type of film they form at the interface between the two phases.

Monomolecular Films—Those surface-active agents which are capable of stabilizing an emulsion do so by forming a monolayer of adsorbed molecules or ions at the oil/water interface (Fig 5). In accordance with Gibbs' law (page 248) the presence of an interfacial excess necessitates a reduction in interfacial tension. This results in a more stable emulsion because of a proportional reduction in the surface free energy. Of itself, this reduction is probably not the main factor promoting stability. More significant is the fact that the droplets are surrounded now by a coherent monolayer which prevents coalescence between approaching droplets. If the emulsifier forming the monolayer is ionized, the presence of strongly charged and mutually repelling droplets increases the stability of the system. With unionized, nonionic surface-active agents, the particles may still carry a charge; this arises from adsorption of a specific ion or ions from solution.

Multimolecular Films—Hydrated lyophilic colloids form multimolecular films around droplets of dispersed oil (Fig 5). The use of these agents has declined in recent years because of the large number of synthetic surface-active agents available which possess well-marked emulsifying properties. While these hydrophilic colloids are adsorbed at an interface (and can be regarded therefore as "surface-active"), they do not cause an appreciable lowering in surface tension. Rather, their efficiency depends on their ability to form strong coherent multimolecular films. These act as a coating around the droplets and render them highly resistant to coalescence, even in the absence of a well-developed surface potential. Furthermore, any hydrocolloid not adsorbed at the interface increases the viscosity of the continuous aqueous phase; this enhances emulsion stability.

Solid Particle Films—Small solid particles that are wetted to some degree by both aqueous and nonaqueous liquid phases act as emulsifying agents. If the particles are too hydrophilic, they remain in the aqueous phase; if too hydrophobic, they are dispersed completely in the oil phase. A second

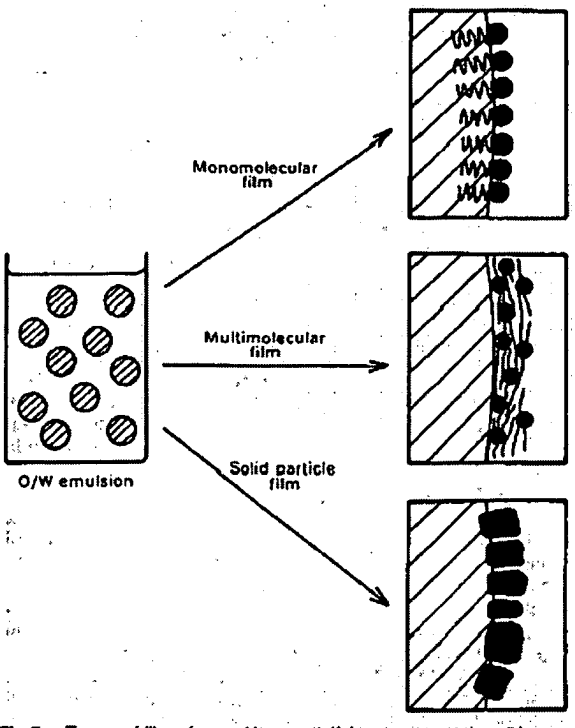


Fig 5. Types of films formed by emulsifying agents at the oil/water interface. Orientations are shown for O/W emulsions. ▨: oil; □: water.

requirement is that the particles are small in relation to the droplets of the dispersed phase (Fig 5).

Chemical Types

Emulsifying agents also may be classified in terms of their chemical structure; there is some correlation between this classification and that based on the mechanism of action. For example, the majority of emulsifiers forming monomolecular films are synthetic, organic materials. Most of the emulsifiers that form multimolecular films are obtained from natural sources and are organic. A third group is composed of solid particles, invariably inorganic, that form films composed of finely divided solid particles.

Accordingly, the classification, adopted divides emulsifying agents into *synthetic*, *natural* and *finely dispersed solids* (Table 3). A fourth group, the *auxiliary materials* (Table 4), are weak emulsifiers. The agents listed are designed to illustrate the various types available; they are not meant to be exhaustive.

Synthetic Emulsifying Agents—This group of surface-active agents which act as emulsifiers may be subdivided into anionic, cationic and nonionic, depending on the charge possessed by the surfactant.

Anionics—In this subgroup the surfactant ion bears a negative charge. The potassium, sodium and ammonium salts of lauric and oleic acid are soluble in water and are good O/W emulsifying agents. They do, however, have a disagreeable taste and are irritating to the gastrointestinal tract; this limits them to emulsions prepared for external use. Potassium laurate, a typical example, has the structure

$$CH_3(CH_2)_{10}COO^- K^+$$

Solutions of alkali soaps have a high pH; they start to precipitate out of solution below pH 10 because the unionized fatty acid is now formed, and this has a low aqueous solubility. Further, the free fatty acid is ineffective as an emulsifier and so emulsions formed from alkali soaps are not stable at pH values less than about 10.

The calcium, magnesium and aluminum salts of fatty acids, often termed the metallic soaps, are water insoluble and result in W/O emulsions.

Another class of soaps are salts formed from a fatty acid and an organic amine such as triethanolamine. While these O/W emulsifiers also are limited to external preparations, their alkalinity is considerably less than that of the alkali soaps and they are active as emulsifiers down to around pH 8. These agents are less irritating than the alkali soaps.

Sulfated alcohols are neutralized sulfuric acid esters of such fatty alcohols as lauryl and cetyl alcohol. These compounds are an important group of pharmaceutical surfactants. They are used chiefly as wetting agents, although they do have some value as emulsifiers, particularly, when used in conjunction with an auxiliary agent.

Sulfonates are a class of compounds in which the sulfur atom is connected directly to the carbon atom, giving the general formula

$$CH_3(CH_2)_nCH_2SO_3^- Na^+$$

A frequently used compound is sodium lauryl sulfate. Sulfonates have a higher tolerance to calcium ions and do not hydrolyze as readily as the sulfates. A widely used surfactant of this type is dioctyl sodium sulfosuccinate.

Cationics—The surface activity in this group resides in the positively charged cation. These compounds have marked bactericidal properties. This makes them desirable in emulsified anti-infective products such as skin lotions and creams. The pH of an emulsion prepared with a cationic emulsifier lies

Table 3—Classification of Emulsifying Agents

Type	Type of film	Examples	
Synthetic (surface-active agents)	Monomolecular	*Anionic:*	*Cationic:*
		Soaps	Quaternary ammonium compounds
		Potassium laurate	Cetyltrimethylammonium bromide
		Triethanolamine stearate	Laurykdimethylbenzylammonium chloride
		Sulfates	*Nonionic:*
		Sodium lauryl sulfate	Polyoxyethylene fatty alcohol ethers
		Alkyl polyoxyethylene sulfates	Sorbitan fatty acid esters
		Sulfonates	Polyoxyethylene sorbitan fatty acid esters
		Dioctyl sodium sulfosuccinate	
Natural	Multimolecular	*Hydrophilic colloids:*	
		Acacia	
		Gelatin	
	Monomolecular	Lecithin	
		Cholesterol	
Finely divided solids	Solid particle	*Colloidal clays:*	
		Bentonite	
		Veegum	
		Metallic hydroxides:	
		Magnesium hydroxide	

Table 4—Auxiliary Emulsifying Agents

Product	Source and composition	Principal use
Cetyl alcohol	Chiefly $C_{16}H_{33}OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Glyceryl monostearate	$C_{17}H_{35}COOCH_2CHOHCH_2OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Methylcellulose	Series of methyl ethers of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Sodium carboxymethylcellulose	Sodium salt of the carboxymethyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions
Stearic acid	A mixture of solid acids from fats, chiefly stearic and palmitic	Lipophilic thickening agent and stabilizer for O/W lotions and ointments. Forms a true emulsifier when reacted with an alkali

in the pH 4–6 ranges. Since this includes the normal pH of the skin, cationic emulsifiers are advantageous in this regard also.

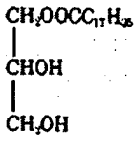
Cationic agents are weak emulsifiers and generally are formulated with a stabilizing or auxiliary emulsifying agent such as cetostearyl alcohol. The only group of cationic agents used extensively as emulsifying agents are the quaternary ammonium compounds. An example is cetyltrimethyl-ammonium bromide.

$$CH_3(CH_2)_{14}CH_2N^+(CH_3)_3\ Br^-$$

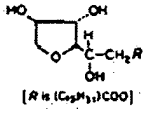
Cationic emulsifiers should not be used in the same formulation with anionic emulsifiers as they will interact. While the incompatibility may not be immediately apparent as a precipitate, virtually all of the desired antibacterial activity will generally have been lost.

Nonionics—These undissociated surfactants find widespread use as emulsifying agents when they possess the proper balance of hydrophilic and lipophilic groups within the molecule. Their popularity is based on the fact that, unlike the anionic and cationic types, nonionic emulsifiers are not susceptible to pH changes and the presence of electrolytes. The number of nonionic agents available is legion; the most frequently used are the glyceryl esters, polyoxyethylene glycol esters and ethers, and the sorbitan fatty acid esters and their polyoxyethylene derivatives.

A glyceryl ester, such as glyceryl monostearate, is too lipophilic to serve as a good emulsifier; it is used widely as an auxiliary agent (Table 4) and has the structure

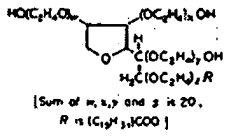


Sorbitan fatty acid esters, such as sorbitan monopalmitate



[R is $(C_{15}H_{31})COO$]

are nonionic oil-soluble emulsifiers that promote W/O emulsions. The polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monopalmitate



[Sum of w, x, y and z is 20. R is $(C_{15}H_{31})COO$]

are hydrophilic water-soluble derivatives that favor O/W emulsions.

Polyoxyethylene glycol esters, such as the monostearate, $C_{17}H_{35}COO(CH_2OCH_2)_nH$, also are used widely.

Very frequently, the best results are obtained from blends of nonionic emulsifiers. Thus, an O/W emulsifier customarily will be used in an emulsion with a W/O emulsifier. When blended properly, the nonionics produce fine-textured stable emulsions.

Natural Emulsifying Agents—Of the numerous emulsifying agents derived from natural (ie, plant and animal) sources, consideration will be given only to acacia, gelatin, lecithin and cholesterol. Many other natural materials are only sufficiently active to function as auxiliary emulsifying agents or stabilizers.

Acacia is a carbohydrate gum that is soluble in water and forms O/W emulsions. Emulsions prepared with acacia are stable over a wide pH range. Because it is a carbohydrate it is necessary to preserve acacia emulsions against microbial attack by the use of a suitable preservative.

Gelatin, a protein, has been used for many years as an emulsifying agent. Gelatin can have two isoelectric points, depending on the method of preparation. So-called Type A gelatin, derived from an acid-treated precursor, has an isoelectric point of between pH 7 and 9. Type B gelatin, obtained from an alkali-treated precursor, has an isoelectric point of approximately pH 5. Type A gelatin acts best as an emulsifier around pH 3, where it is positvely charged; on the other hand, Type B gelatin is best used around pH 8, where it is negatively charged. The question as to whether the gelatin is positively or negatively charged is fundamental to the stability of the emulsion when other charged emulsifying agents are present. In order to avoid an incompatibility, all emulsifying agents should carry the same sign. Thus, if gums (such as tragacanth, acacia or agar) which are negatively charged are to be used with gelatin, Type B material should be used at an alkaline pH. Under these conditions the gelatin is similarly negatively charged.

Lecithin is a phospholipid which, because of its strongly hydrophilic nature, produces O/W emulsions. It is liable to microbial attack and tends to darken on storage.

Cholesterol is a major constituent of wool alcohols, obtained by the saponification and fractionation of wool fat. It is cholesterol that gives wool fat its capacity to absorb water and form a W/O emulsion.

Finely Dispersed Solids—This group of emulsifiers forms particulate films around the dispersed droplets and produces emulsions which, while coarse-grained, have considerable physical stability. It appears possible that any solid can act as an emulsifying agent of this type, provided it is reduced to a sufficiently fine powder. In practice the group of compounds used most frequently are the colloidal clays.

Bentonite is a white to gray, odorless and tasteless powder that swells in the presence of water to form a translucent suspension with a pH of about 9. Depending on the sequence of mixing it is possible to prepare both O/W and W/O emulsions. When an O/W emulsion is desired, the bentonite is first dispersed in water and allowed to hydrate so as to form a magma. The oil phase is then added gradually with constant tituration. Since the aqueous phase is always in excess, the O/W emulsion type is favored. To prepare a W/O emulsion, the bentonite is first dispersed in oil; the water is then added gradually.

While Veegum is used as a solid particle emulsifying agent, it is employed most extensively as a stabilizer in cosmetic lotions and creams. Concentrations of less than 1% Veegum will stabilize an emulsion containing anionic or nonionic emulsifying agents.

Auxiliary Emulsifying Agents—Included under this heading are those compounds which are normally incapable themselves of forming stable emulsions. Their main value lies in their ability to function as thickening agents and thereby help stabilize the emulsion. Agents in common use are listed in Table 4.

Emulsifying Agents and Emulsion Type

For a molecule, ion, colloid or particle to be active as an emulsifying agent, it must have some affinity for the interface between the dispersed phase and the dispersion medium. With the mono- and multilayer films the emulsifier is in solution and, therefore, must be soluble to some extent in one or both of the phases. At the same time it must not be overly soluble in either phase, otherwise it will remain in the bulk of that phase and not be adsorbed at the interface. This balanced affinity for the two phases also must be evident with finely divided solid particles used as emulsifying agents. If their affinity, as evidenced by the degree to which they are wetted, is either predominantly hydrophilic or hydrophobic, they will not function as effective wetting agents.

The great majority of the work on the relation between emulsifier and emulsion type has been concerned with surface-active agents that form interfacial monolayers. The present discussion, therefore, will concentrate on this class of agents.

Hydrophile-Lipophile Balance—As the emulsifier becomes more hydrophilic, its solubility in water increases and the formation of an O/W emulsion is favored. Conversely, W/O emulsions are favored with the more lipophilic emulsifiers. This led to the concept that the type of emulsion is related to the balance between hydrophilic and lipophilic solution tendencies of the surface-active emulsifying agent.

Griffin[12] developed a scale based on the balance between these two opposing tendencies. This so-called *HLB scale* is a numerical scale, extending from 1 to approximately 50. The more hydrophilic surfactants have high HLB numbers (in excess of 10), while surfactants with HLB numbers from 1 to 10 are considered to be lipophilic. Surfactants with a proper balance in their hydrophilic and lipophilic affinities are effective emulsifying agents since they concentrate at the oil/water interface. The relationship between HLB values and the application of the surface-active agent is shown in Table 5. Some commonly used emulsifiers and their HLB numbers are listed in Table 6. The utility of the HLB system in rationalizing the choice of emulsifying agents when formulating an emulsion will be discussed in a later section.

Rate of Coalescence and Emulsion Type—Davies[9] indicated that the type of emulsion produced in systems prepared by shaking is controlled by the relative coalescence rates of oil droplets dispersed in the oil. Thus, when a mixture of oil and water is shaken together with an emulsifying agent, a multiple dispersion is produced initially which contains oil dispersed in water and water dispersed in oil (Fig 4). The type of the final emulsion which results depends on whether the water or the oil droplets coalesce more rapidly. If the O/W coalescence rate (Rate 1) is much greater than W/O coalescence rate (Rate 2), a W/O emulsion is formed since the dispersed water droplets are more stable than the dispersed oil droplets. Conversely, if Rate 2 is significantly faster than Rate 1, the final emulsion is an O/W dispersion because the oil droplets are more stable.

Table 5—Relationship between HLB Range and Surfactant Application

HLB range	Use
0–3	Antifoaming agents
4–6	W/O emulsifying agents
7–9	Wetting agents
8–18	O/W emulsifying agents
13–15	Detergents
10–18	Solubilizing agents

Table 6—Approximate HLB Values for a Number of Emulsifying Agents

Generic or chemical name	HLB
Sorbitan trioleate	1.8
Propylene glycol monostearate	3.4
Glycerol monostearate (non self-emulsifying)	3.8
Propylene glycol monolaurate	4.5
Sorbitan monostearate	4.7
Glyceryl monostearate (self-emulsifying)	5.5
Sorbitan monolaurate	8.6
Polyoxyethylene-4-lauryl ether	9.5
Polyethylene glycol 400 monostearate	11.6
Polyoxyethylene-4-sorbitan monolaurate	13.3
Polyoxyethylene-20-sorbitan monopalmitate	15.6
Polyoxyethylene-40-stearate	16.9
Sodium oleate	18.0
Sodium lauryl sulfate	40.0

According to Davies, the rate at which oil globules coalesce when dispersed in water is given by the expression

$$\text{Rate 1} = C_1 e^{-W_1/RT} \qquad (7)$$

The term C_1 is a collision factor which is directly proportional to the phase volume of the oil relative to the water, and is an inverse function of the viscosity of the continuous phase (water). W_1 defines an energy barrier made up of several contributing factors that must be overcome before coalescence can take place. First, it depends on the electrical potential of the dispersed oil droplets, since this affects repulsion. Second, with an O/W emulsion, the hydrated layer surrounding the polar portion of emulsifying agent must be broken down before coalescence can occur. This hydrated layer is probably around 10 Å thick with a consistency of butter. Finally, the total energy barrier depends on the fraction of the interface covered by the emulsifying agent.

Equation 8 describes the rate of coalescence of water globules dispersed in oil, namely

$$\text{Rate 2} = C_2 e^{-W_2/RT} \qquad (8)$$

Here, the collision factor C_2 is a function of the water/oil phase volume ratio divided by the viscosity of the oil phase. The energy barrier W_2 is, as before, related to the fraction of the interface covered by the surface-active agent. Another contributing factor is the number of —CH_2— groups in the emulsifying agent; the longer the alkyl chain of the emulsifier, the greater the gap that has to be bridged if one water droplet is to combine with a second drop.

Davies[9] showed that the HLB concept is related to the distribution characteristics of the emulsifying agent between the two immiscible phases. An emulsifier with an HLB of less than 7 will be preferentially soluble in the oil phase and will favor formation of a W/O emulsion. Surfactants with an HLB value in excess of 7 will be distributed in favor of the aqueous phase and will promote O/W emulsions.

Preparation of Emulsions

Several factors must be taken into account in the successful preparation and formulation of emulsified products. Usually, the type of emulsion (ie, O/W or W/O) is specified; if not, it probably will be implied from the anticipated use of the product. The formulator's attention is focused primarily on the selection of the emulsifying agent, or agents, necessary to achieve a satisfactory product. No incompatibilities should occur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the product should be prepared in such a way as not to prejudice the formulation.

The selection of the emulsifying agent, or agents, is of prime importance in the successful formulation of an emulsion. In addition to its emulsifying properties, the pharmacist must ensure that the material chosen is nontoxic and that the taste, odor and chemical stability are compatible with the product. Thus, an emulsifying agent which is entirely suitable for inclusion in a skin cream may be unacceptable in the formulation of an oral preparation due to its potential toxicity. This consideration is most important when formulating intravenous emulsions.

The HLB System—With the increasing number of available emulsifiers, particularly the nonionics, the selection of emulsifiers for a product was essentially a trial-and-error procedure. Fortunately, the work of Griffin[12,13] provided a logical means of selecting emulsifying agents. Griffin's method, based on the balance between the hydrophilic and lipophilic portions of the emulsifying agent, is now widely used and has come to be known as the *HLB system*. It is used most in the rational selection of combinations of nonionic emulsifiers, and we shall limit our discussion accordingly.

As shown in Table 5, if an O/W emulsion is required, the formulator should use emulsifiers with an HLB in the range of 8–18. Emulsifiers with HLB values in the range of 4–6 are given consideration when a W/O emulsion is desired. Some typical examples are given in Table 6.

Another factor is the presence or absence of any polarity in the material being emulsified, since this will affect the polarity required in the emulsifier. Again, as a result of extensive experimentation, Griffin evolved a series of "required HLB" values; ie, the HLB value required by a particular material if it is to be emulsified effectively. Some values for oils and related materials are contained in Table 7. Naturally, the required HLB value differs depending on whether the final emulsion is O/W or W/O.

Fundamental to the utility of the HLB concept is the fact that the HLB values are algebraically additive. Thus, by using a low HLB surfactant with one having a high HLB it is possible to prepare blends having HLB values intermediate between those of the two individual emulsifiers. The following formula serves as an example.

O/W Emulsion

Liquid petrolatum (Required HLB 10.5)	50 g
Emulsifying agents	5 g
Sorbitan monooleate (HLB 4.3)	
Polyoxyethylene 20 sorbitan monoleate (HLB 15.0)	
Water, qs	100 g

By simple algebra it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of polyoxyethylene 20 sorbitan monooleate will result in a mixed emulsifying agent having the required HLB of 10.5. Since the formula calls for 5 g, the required weights are 2.1 g and 2.9 g, respectively. The oil-soluble sorbitan monooleate is dissolved in the oil and heated to 75°; the water-soluble polyoxyethylene 20 sorbitan monooleate is added to the aqueous phase which is heated to 70°. At this point the oil phase is mixed with the aqueous phase and the whole stirred continuously until cool.

Table 7—Required HLB Values for Some Common Emulsion Ingredients

Substance	W/O	O/W
Acid, stearic	—	17
Alcohol, cetyl	—	13
Lanolin, anhydrous	8	15
Oil, cottonseed	—	7.5
mineral oil, light	4	10–12
mineral oil, heavy	4	10.5
Wax, beeswax	5	10–16
microcrystalline	—	9.5
paraffin	—	9

Table 8—Nonionic Blends having HLB Values of 10.5

Surfactant blend	HLB	Required amounts (%) to give HLB = 10.5
Sorbitan tristearate	2.1	34.4
Polyoxyethylene 20 sorbitan monostearate	14.9	65.6
Sorbitan monopalmitate	6.7	57.3
Polyoxyethylene 20 sorbitan monopalmitate	15.6	42.7
Sorbitan sesquioleate	3.7	48.5
Polyoxyethylene lauryl ether	16.9	51.5

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. Table 8 shows the various proportions required, using other pairs of emulsifying agents, to form a blend of HLB 10.5. When carrying out preliminary investigations with a particular material to be emulsified, it is advisable to try several pairs of emulsifying agents. Based on an evaluation of the emulsions produced, it becomes possible to choose the best combination.

Occasionally, the required HLB of the oil may not be known, in which case it becomes necessary to determine this parameter. Various blends are prepared to give a wide range of HLB mixtures and emulsions are prepared in a standardized manner. The HLB of the blend used to emulsify the best product, selected on the basis of physical stability, is taken to be the required HLB of the oil. The experiment should be repeated using another combination of emulsifiers to confirm the value of the required HLB of the oil to within, say, ±1 HLB unit.

There are methods for finding the HLB value of a new surface-active agent. Griffin[13] developed simple equations which can be used to obtain an estimate with certain compounds. It has been shown that the ability of a compound to spread at a surface is related to its HLB. In another approach a linear relation between HLB and the logarithm of the dielectric constant for a number of nonionic surfactants has been observed. An interesting approach has been developed by Davies[9] and is related to his studies on the relative rates of coalescence of O/W and W/O emulsions (page 287). According to Davies, hydrophilic groups on the surfactant molecule make a positive contribution to the HLB number, whereas lipophilic groups exert a negative effect. Davies calculated these contributions and termed them HLB Group Numbers (Table 9). Provided the molecular structure of the

Table 9—HLB Group Numbers[14]

	Group number
Hydrophilic groups	
$-SO_4^-Na^+$	38.7
$-COO^-K^+$	21.1
$-COO^-Na^+$	19.1
N (tertiary amine)	9.4
Ester (sorbitan ring)	6.8
Ester (free)	2.4
—COOH	2.1
Hydroxyl (free)	1.9
—O—	1.3
Hydroxyl (sorbitan ring)	0.5
Lipophilic groups	
—CH—	
$-CH_2-$	
CH_3-	−0.475
=CH—	
Derived groups	
$-(CH_2-CH_2-O)-$	+0.33
$-(CH_3-CH_2-CH_2-O)-$	−0.15

surfactant is known, one simply adds the various group numbers in accordance with the following formula:

$$HLB = \Sigma(\text{hydrophilic group numbers}) - m(\text{group number}/\text{—}CH_2\text{—group}) + 7$$

where m is the number of —CH_2— groups present in the surfactant. Poor agreement is found between the HLB values calculated by the use of group numbers and the HLB values obtained using the simple equations developed by Griffin. However, the student should realise that the absolute HLB values *per se* are of limited significance. The utility of the HLB approach (using values calculated by either Griffin's or Davies' equations) is to (1) provide the formulator with an idea of the relative balance of hydrophilicity and lipophilicity in a particular surfactant and (2) relate that surfactant's emulsifying and solubilizing properties to other surfactants. The formulator still needs to confirm experimentally that a particular formulation will produce a stable emulsion.

Later, Davies and Rideal[14] attempted to relate HLB to the C_{water}/C_{oil} partition coefficient and found good agreement for a series of sorbitan surfactants. Schott[15] showed, however, that the method does not apply to polyoxyethylated octylphenol surfactants. Schott concluded that "so far, the search for a universal correlation between HLB and another property of the surfactant which could be determined more readily than HLB has not been successful."

The HLB system gives no information as to the *amount* of emulsifier required. Having once determined the correct blend, the formulator must prepare another series of emulsions, all at the same HLB, but containing increasing concentrations of the emulsifier blend. Usually, the minimum concentration giving the desired degree of physical stability is chosen.

Mixed Emulsifying Agents—Emulsifying agents are frequently used in combination since a better emulsion usually is obtained. This enhancement may be due to several reasons, one or more of which may be operative in any one system. Thus, the use of a blend or mixture of emulsifiers may (1) produce the required hydrophile-lipophile balance in the emulsifier, (2) enhance the stability and cohesiveness of the interfacial film and (3) affect the consistency and feel of the product.

The first point has been considered in detail in the previous discussion of the HLB system.

With regard to the second point, Schulman and Cockbain in 1940 showed that combinations of certain amphiphiles formed stable films at the air/water interface. It was postulated that the complex formed by these two materials (one, oil-soluble; the other, water-soluble) at the air/water interface was also present at the O/W interface. This interfacial complex was held to be responsible for the improved stability. For example, sodium cetyl sulfate, a moderately good O/W emulsifier, and elaidyl alcohol or cholesterol, both stabilizers for W/O emulsions, show evidence of an interaction at the air/water interface. Furthermore, an O/W emulsion prepared with sodium cetyl sulfate and elaidyl alcohol is much more stable than an emulsion prepared with sodium cetyl sulfate alone.

Elaidyl alcohol is the *trans* isomer. When oleyl alcohol, the *cis* isomer, is used with sodium cetyl sulfate, there is no evidence of complex formation at the air/water interface. Significantly, this combination does not produce a stable O/W emulsion either. Such a finding strongly suggests that a high degree of molecular alignment is necessary at the O/W interface to form a stable emulsion.

When using combinations of emulsifiers, care must be taken to ensure their compatibility, as charged emulsifying agents of opposite sign are likely to interact and coagulate when mixed.

Method of Preparation

Different methods are employed, depending on the type of emulsifying agent used and the scale of manufacture. Traditionally, the mortar and pestle was used for the small scale preparation of emulsions stabilized by the presence of such agents as acacia and tragacanth. However, the use of these agents has declined drastically in recent years and, as a result, so too, has the use of the mortar and pestle. Refer to RPS-18, page 306 for details of the mortar and pestle method.

An increasing number of emulsions are being formulated with synthetic emulsifying agents, especially of the nonionic type. The components in such a formulation are separated into those that are oil-soluble and those that are water-soluble. These are dissolved in their respective solvents by heating to about 70 to 75°. When solution is complete, the two phases are mixed and the product is stirred until cool. This method, which requires nothing more than two beakers, a thermometer and a source of heat, is necessarily used in the preparation of emulsions containing waxes and other high-melting-point materials that must be melted before they can be dispersed in the emulsion. The relatively simple methodology involved in the use of synthetic surfactant-type emulsifiers is one factor which has led to their widespread use in emulsion preparation. This, in turn, has led to a decline in the use of the natural emulsifying agents.

With hand homogenizers an initial rough emulsion is formed by trituration in a mortar or shaking in a bottle. The rough emulsion is then passed several times through the homogenizer. A reduction in particle size is achieved as the material is forced through a narrow aperture under pressure. A satisfactory product invariably results from the use of a hand homogenizer and overcomes any deficiencies in technique. Should the homogenizer fail to produce an adequate product, the formulation, rather than the technique, should be suspected.

For a discussion of the techniques and equipment used in the large-scale manufacture of emulsions, see Chapter 86.

Stability of Emulsions

There are several criteria which must be met in a well-formulated emulsion. Probably the most important and most readily apparent requirement is that the emulsion possess adequate physical stability; without this, any emulsion soon will revert back to two separate bulk phases. In addition, if the emulsified product is to have some antimicrobial activity (eg, a medicated lotion), care must be taken to ensure that the formulation possesses the required degree of activity. Frequently, a compound exhibits a lower antimicrobial activity in an emulsion than, say, in a solution. Generally, this is because of partitioning effects between the oil and water phases, which cause a lowering of the "effective" concentration of the active agent. Partitioning has also to be taken into account when considering preservatives to prevent microbiological spoilage of emulsions. Finally, the chemical stability of the various components of the emulsion should receive some attention, since such materials may be more prone to degradation in the emulsified state than when they exist as a bulk phase.

In the present discussion, detailed consideration will be limited to the question of physical stability. Reviews of this topic have been published by Garrett[16] and Kitchener and Mussellwhite.[17] For information on the effect that emulsification can have on the biologic activity and chemical stability of materials in emulsions, see Wedderburn,[18] Burt[19] and Swarbrick.[20]

The theories of emulsion stability have been discussed by Eccleston[21] in an attempt to understand the situation in both a simple O/W emulsion and complex commercial systems. A recent review by the same author[8] has discussed the stability of multiple phase emulsions and the role of bilayer gels and liquid crystalline phases on the physical stability of these systems.

The three major phenomena associated with physical stability are

1. The upward or downward movement of dispersed droplets relative to the continuous phase, termed *creaming* or *sedimentation*, respectively.

2. The aggregation and possible coalescence of the dispersed droplets to reform the separate, bulk phases.
3. Inversion, in which an O/W emulsion inverts to become a W/O emulsion and *vice versa*.

Creaming and Sedimentation—Creaming is the upward movement of dispersed droplets relative to the continuous phase, while sedimentation, the reverse process, is the downward movement of particles. In any emulsion one process or the other takes place, depending on the densities of the disperse and continuous phases. This is undesirable in a pharmaceutical product where homogeneity is essential for the administration of the correct and uniform dose. Furthermore, creaming, or sedimentation, brings the particles closer together and may facilitate the more serious problem of coalescence.

The rate at which a spherical droplet or particle sediments in a liquid is governed by Stokes' law (Eq 3). While other equations have been developed for bulk systems, Stokes' equation is still useful since it points out the factors that influence the rate of sedimentation or creaming. These are the diameter of the suspended droplets, the viscosity of the suspending medium and the difference in densities between the dispersed phase and the dispersion medium.

Usually, only the use of the first two factors is feasible in affecting creaming or sedimentation. Reduction of particle size contributes greatly toward overcoming or minimizing creaming, since the rate of movement is a square-root function of the particle diameter. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm. The most frequently used approach is to raise the viscosity of the continuous phase, although this can be done only to the extent that the emulsion still can be removed readily from its container and spread or administered conveniently.

Aggregation and Coalescence—Even though creaming and sedimentation are undesirable, they do not necessarily result in the breakdown of the emulsion, since the dispersed droplets retain their individuality. Furthermore, the droplets can be redispersed with mild agitation. More serious to the stability of an emulsion are the processes of aggregation and coalescence. In aggregation (flocculation) the dispersed droplets come together but do not fuse. Coalescence, the complete fusion of droplets, leads to a decrease in the number of droplets and the ultimate separation of the two immiscible phases. Aggregation precedes coalescence in emulsions; however, coalescence does not necessarily follow from aggregation. Aggregation is, to some extent, reversible. While not as serious as coalescence, it will accelerate creaming or sedimentation, since the aggregate behaves as a single drop.

While aggregation is related to the electrical potential on the droplets, coalescence depends on the structural properties of the interfacial film. In an emulsion stabilized with surfactant-type emulsifiers forming monomolecular films, coalescence is opposed by the elasticity and cohesiveness of the films sandwiched between the two droplets. In spite of the fact that two droplets may be touching, they will not fuse until the interposed films thin out and eventually rupture. Multilayer and solid-particle films confer on the emulsion a high degree of resistance to coalescence, due to their mechanical strength. Even greater resistance to coalescence occurs when liquid crystalline or gel structures are present in the emulsion.

Particle-size analysis can reveal the tendency of an emulsion to aggregate and coalesce long before any visible signs of instability are apparent. The methods available have been reviewed by Groves and Freshwater.[22]

Inversion—An emulsion is said to invert when it changes from an O/W to a W/O emulsion, or *vice versa*. Inversion sometimes can be brought about by the addition of an electrolyte or by changing the phase-volume ratio. For example, an O/W emulsion having sodium stearate as the emulsifier can be inverted by the addition of calcium chloride, because the calcium stearate formed is a lipophilic emulsifier and favors the formation of a W/O product.

Inversion often can be seen when an emulsion, prepared by heating and mixing the two phases, is being cooled. This takes place presumably because of the temperature-dependent changes in the solubilities of the emulsifying agents. The phase inversion temperature, or PIT of nonionic surfactants has been shown by Shinoda and Kunieda[23] to be influenced by the HLB number of the surfactant. The higher the PIT value, the greater the resistance to inversion.

Apart from work on PIT values, little quantitative work has been carried out on the process of inversion; nevertheless, it would appear that the effect can be minimized by using the proper emulsifying agent in an adequate concentration. Wherever possible, the volume of the dispersed phase should not exceed 50% of the total volume of the emulsion.

Bioavailability from Coarse Dispersions

All dosage forms must be capable of releasing the drug in a known and consistent manner following administration to the patient. Both the rate and extent of release are important. Ideally, the extent of release should approach 100%, while the rate of release should reflect the desired properties of the dosage form. For example, with products designed to have a rapid onset of activity, the release of drug should be immediate. With a long-acting product, the release should take place over several hours, or days, depending on the type of product used. The rate and extent of drug release should be reproducible from batch to batch of the product, and should not change during shelf-life.

The principles on which biopharmaceutics is based are dealt with in some detail in Chapters 41 to 43. While most published work in this area has been concerned with the bioavailability of solid dosage forms administered by the oral route, the rate and extent of release from both suspensions and emulsions is important and so will be considered in some detail.

Bioavailability from Suspensions—Suspensions of a drug may be expected to demonstrate improved bioavailability compared to the same drug formulated as a tablet or capsule. This is because the suspension already contains discrete drug particles, whereas tablet dosage forms must invariably undergo disintegration in order to maximize the necessary dissolution process. Frequently, antacid suspensions are perceived as being more rapid in action and therefore more effective than an equivalent dose in the form of tablets. Bates *et al*[24] observed that a suspension of salicylamide was more rapidly bioavailable, at least during the first hour following administration, than two different tablet forms of the drug; these workers were also able to demonstrate a correlation between the initial *in vitro* dissolution rates for the several dosage forms studied and the initial rates of *in vivo* absorption. A similar argument can be developed for hard gelatin capsules, where the shell must rupture or dissolve before drug particles are released and can begin the dissolution process. Such was observed by Antal *et al*[25] in a study of the bioavailability of several doxycycline products, including a suspension and hard gelatin capsules. Sansom *et al*[26] found mean plasma phenytoin levels higher after the administration of a suspension than when an equivalent dose was given as either tablets or capsules. It was suggested that this might have been due to the suspension having a smaller particle size.

In common with other products in which the drug is present in the form of solid particles, the rate of dissolution, and thus potentially the bioavailability of the drug in a suspension, can

be affected by such factors as particle size and shape, surface characteristics, and polymorphism. Strum *et al*[27] conducted a comparative bioavailability study involving two commercial brands of sulfamethiazole suspension (Product A and Product B). Following administration of the products to 12 normal subjects and taking blood samples at predetermined times over a period of 10 hours, the workers found no statistically significant difference in the extent of drug absorption from the two suspensions. The absorption rate, however, differed, and from *in vitro* studies it was concluded that product A dissolved faster than product B and that the former contained more particles of smaller size than the latter, differences that may be responsible for the more rapid dissolution of particles in product A. Product A also provided higher serum levels in *in vivo* tests half an hour after administration. The results showed that the rate of absorption of sulfamethiazole from a suspension depended on the rate of dissolution of the suspended particles, which in turn was related to particle size. Previous studies[28,29] have shown the need to determine the dissolution rate of suspensions in order to gain information as to the bioavailability of drugs from this type of dosage form.

The viscosity of the vehicle used to suspend the particles has been found to have an effect on the rate of absorption of nitrofurantoin but not the total bioavailability. Thus Soci and Parrott were able to maintain a clinically acceptable urinary nitrofurantoin concentration for an additional two hours by increasing the viscosity of the vehicle.[30]

Bioavailability from Emulsions—There are indications that improved bioavailability may result when a poorly absorbed drug is formulated as an orally administered emulsion. However, little study appears to have been made in direct comparison of emulsions and other dosage forms such as suspensions, tablets and capsules; thus it is not possible to draw unequivocal conclusions as to advantages of emulsions. If a drug with low aqueous solubility can be formulated so as to be in solution in the oil phase of an emulsion, its bioavailability may be enhanced. It must be recognized, however, that the drug in such a system has several barriers to pass before it arrives at the mucosal surface of the gastrointestinal tract. For example, with an oil-in-water emulsion, the drug must diffuse through the oil globule and then pass accross the oil/water interface. This may be a difficult process, depending on the characteristics of the interfacial film formed by the emulsifying agent. In spite of this potential drawback, Wagner *et al*[31] found that indoxole, a nonsteroidal anti-inflammatory agent, was significantly more bioavailable in an oil-in-water emulsion than in either a suspension or a hard gelatin capsule. Bates and Sequeira[32] found significant increases in maximum plasma levels and total bioavailabilty of micronized griseofulvin when formulated in a corn oil/water emulsion. In this case, however, the enhanced effect was not due to emulsification of the drug in the oil phase *per se* but more probably because of the linoleic and oleic acids present having a specifical effect on gastrointestinal motility.

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Description—Colorless or pale yellow, oily liquid, with a characteristic nutty odor and a bland taste; specific gravity 0.912 to 0.920.

Solubility—Very slightly soluble in alcohol; miscible with ether, chloroform or carbon disulfide.

Uses—A *solvent* in preparing oil solutions for injection (page 1549). It also is used for making liniments, ointments, plasters and soaps, as a substitute for olive oil.

Sesame Oil

Teel Oil; Benne Oil; Gingili Oil

The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* Linné (Fam *Pedaliaceae*).

Description—Pale yellow, almost odorless, oily liquid with a bland taste; specific gravity 0.916 to 0.921.

Solubility—Slightly soluble in alcohol; miscible with ether, chloroform, solvent hexane or carbon disulfide.

Uses—A *solvent* and *vehicle* in official injections. It is used much like olive oil both medicinally and for food. It does not readily turn rancid. It also is used in the manufacture of cosmetics, iodized oil, liniments, ointments and oleomargarine.

Water for Injection

Water purified by distillation or by reverse osmosis. It contains no added substance.

Caution—It is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render it sterile and thereafter protect it from microbial contamination.

Description—Clear, colorless, odorless liquid.

Uses—*Pharmaceutic aid* (vehicle and solvent).

Bacteriostatic Water for Injection

Sterile water for injection containing one or more suitable antimicrobial agents.

Note—Use it with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Uses—*Sterile vehicle* for parenteral preparations.

Sterile Water for Injection

Water for Parenterals

Water for injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Description—Clear, colorless, odorless, liquid.

Uses—For the preparation of *all aqueous parenteral solutions*, including those used in *animal assays*. See page 1526 for a detailed discussion.

Sterile Water for Irrigation

Water for injection that has been sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Description—Clear, colorless, odorless liquid.

Uses—An *irrigating solution*.

Emulsifying and Suspending Agents

An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid that is immiscible with the first liquid. Emulsions are formed and stabilized with the help of emulsifying agents, which are surfactants and/or viscosity-producing agents. A suspension is defined as a preparation containing finely divided insoluble material suspended in a liquid medium. The presence of a suspending agent is required to overcome agglomeration of the dispersed particles and to increase the viscosity of the medium so that the particles settle more slowly. Emulsifying and suspending agents are used extensively in the formulation of elegant pharmaceutical preparations for oral, parenteral and external use. For the theoretical and practical aspects of emulsions the interested reader is referred to pages 283 and 1395. More detailed information on the use of suspending agents is given on page 1395.

Acacia

Gum Arabic

The dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or of other related African species of *Acacia* (Fam *Leguminosae*).

Constituents—Principally calcium, magnesium and potassium salts of the polysaccharide *arabic acid*, which on acid hydrolysis yields L-arabinose, L-rhamnose, D-galactose and an aldobionic acid containing D-glucuronic acid and D-galactose.

Description—*Acacia:* Spheroidal tears up to 32 mm in diameter or angular fragments of white to yellowish white color; translucent or somewhat opaque; very brittle; almost odorless; produces a mucilaginous sensation on the tongue. *Flake Acacia:* White to yellowish white, thin flakes. *Powdered Acacia:* White to yellowish white, angular microscopic fragments. *Granular Acacia:* White to pale yellowish white, fine granules. *Spray-dried Acacia:* White to off-white compacted microscopic fragments or whole spheres.

Solubility—Insoluble in alcohol, but almost completely soluble in twice its weight of water at room temperature; the resulting solution flows readily and is acid to litmus.

Incompatibilities—*Alcohol or alcoholic solutions* precipitate acacia as a stringy mass when the alcohol amounts to more than about 35% of the total volume. Solution is effected by dilution with water. The mucilage is destroyed through precipitation of the acacia by *heavy metals*. *Borax* also causes a precipitation which is prevented by glycerin. It contains calcium and, therefore, possesses the incompatibilities of this ion.

It contains a *peroxidase* which acts as an oxidizing agent and produces colored derivatives of *aminopyrine, antipyrine, cresol, guaiacol, phenol, tannin, thymol, vanillin* and other substances. Among the alkaloids affected are *atropine, apomorphine, cocaine, homatropine, hyoscyamine, morphine, physostigmine* and *scopolamine*. A partial destruction of the alkaloid occurs in the reaction. Heating the solution of acacia for a few minutes at 100° destroys the peroxidase and the color reactions are avoided.

Uses—Extensively as a *suspending agent* for insoluble substances in water (page 1515), in the preparation of emulsions (pages 282 and 1509) and for making pills and troches (page 1648).

It is used for its *demulcent* action in inflammations of the throat or stomach.

Its solutions should not be used as a substitute for serum protein in the treatment of *shock* and as a *diuretic* in hypoproteinemic edema, since it produces serious syndromes that may result in death.

Acacia Mucilage [Mucilage of Gum Arabic]—*Preparation:* Place acacia (in small fragments, 350 g) in a graduated bottle having a wide mouth and a capacity not greatly exceeding 1000 mL, wash the drug with cold purified water, allow it to drain and add enough warm purified water, in which benzoic acid (2 g) has been dissolved, to make the product measure 1000 mL. After stoppering, lay the bottle on its side, rotate it occasionally, and when the acacia has dissolved strain the mucilage. *It also may be prepared as follows:* dissolve benzoic acid (2 g) in purified water (400 mL) with the aid of heat, and add the solution to powdered or granular acacia (350 g), in a mortar, triturating until the acacia is dissolved. Then add sufficient purified water to make the product measure 1000 mL, and strain if necessary. This second method is primarily for extemporaneous preparation. *Uses:* A *demulcent* and a *suspending agent*. It also has been employed as an *excipient* in making pills and troches, and as an *emulsifying agent* for cod liver oil and other substances. *Caution—It must be free from mold or any other indication of decomposition.*

Agar

Agar-Agar; Vegetable Gelatin; Geloso; Chinese or Japanese Gelatin

The dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gaillon (Fam *Gelidiaceae*), *Gracilaria confervoides* (Linné) Greville (Fam *Sphaerococcaceae*) and related red algae (Class *Rhodophyceae*).